Studies on the assessment and management of chronic obstructive pulmonary disease

a thesis submitted by Professor Peter M A Calverley for the degree of Doctor of Science in the University of Edinburgh

DECLARATION

This thesis has been composed by the candidate himself. The work presented herein was conducted by the candidate or, as indicated in the thesis and the publications which comprise the thesis, the candidate made a substantial contribution to the design, conduct analysis and publication of the studies.

This thesis is not under consideration for the award of any other degree at the University of Edinburgh or at any other institution.

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) has been and remains a major cause of morbidity and mortality across the world. The studies reported in this thesis describe some of the important concepts which have been tested and translated into routine clinical practice in the last 3 decades. We have now clarified the reflex mechanisms underlying persistent cough in COPD, defined the non-specific nature of the sensation of breathlessness in COPD and established that sleep quality is poor in hypoxaemic patients. Secondary polycythaemia is strongly related to carbon monoxide exposure from cigarettes which can also impair exercise tolerance. However the principal reason for exercise limitation in COPD patients is dynamic hyperinflation together with the response of the chest wall muscles to changing lung volume. Defining bronchodilator responsive patients is difficult as the chance of being classified as a responder varies with random fluctuations in baseline FEV_1. Expiratory flow limitation at rest is a useful descriptive variable in characterising COPD but is not a predictor of response to bronchodilator drugs.

COPD exacerbations are still defined by symptom change which does not always agree with the use of therapy, the commonest outcome reported in clinical trials. However events defined by health care use show a consistent pattern over time and patients who exacerbate often in one year are highly likely to do so in subsequently. Exacerbations are associated with worsening lung mechanics and increased operating lung volume which decreases as the episode resolves. Oral corticosteroids hasten the resolution of these episodes. However hyperglycaemia in patients with respiratory failure is a poor prognostic sign despite non-invasive ventilation.

Long-acting inhaled bronchodilators like tiotropium have a sustained bronchodilator effect over the 24 hour day but this does not abolish the normal circadian variation in lung function. Anti-inflammatory therapy with inhaled corticosteroids can reduce exacerbation numbers and improve health status. An effect on mortality has not been conclusively established but seems possible while all treatments so far tested which ameliorate symptoms and reduce exacerbations seem to modify decline in lung function. Another anti-inflammatory agent the PDEIV inhibitor roflumilast has similar effects on exacerbation rate and lung function and may be additive in action. Other non-medical therapy such as heliox can substantially increase exercise performance but are not yet practical for routine use. Rehabilitation, by contrast, can dramatically improve exercise capacity without changing daily activity levels. Despite concerns to the contrary all existing drug treatment is well tolerated and safe.

Future studies will need to address earlier intervention not only with smoking cessation –a key intervention of itself – but also with other probably anti-inflammatory therapy which can prevent disease progression and potentially limit the development of co-morbidities. Improvement in patients with more established disease is more likely to follow from the better delivery of the therapy we already possess rather than reversing well established pathology which remains a distant goal at present.

Acknowledgements

The work in this thesis was conducted by the candidate or by members of his research group under his direction or as part of clinical trials which he helped devise, lead and analyse.

This thesis is the culmination of many years spent trying to conduct clinically relevant but scientifically rigorous research. The work began with the example of the late Sir John Crofton, was fired by the passion for applied science of the late Professor David Flenley and always tried to keep its focus on the problems of patients inspired by the example of Dr Andrew Douglas, the best clinical doctor I have known. I have been more than fortunate in my teachers and what physiology I have understood is due to the time I spent with Drs Joseph Milic –Emili and Peter Macklem in Montreal and Prof Neil Pride in the UK. I have learnt an enormous amount about medicine and life from my colleagues in Edinburgh, Liverpool and in the many centres around the world where I have developed such fruitful collaborations. A special mention is due to my younger colleagues in Liverpool, Drs Lisa Davies, Nikki Stevenson and Paul Walker who have worked tirelessly to deliver complex clinical and physiological studies and also to my co-workers in Milan, Drs Andrea Aliverti and Raffaele Dellaca for the energy and detailed knowledge of bioengineering. I am grateful to my many co-workers for their enthusiasm and continuing insight into all aspects of what we do together and in particular to Prof Wisia Wedzicha for her commitment to understanding COPD exacerbations, Prof Paul Jones who taught me what little I know about health status measurement and how to critically evaluate statistical methods in clinical trials and Prof Jorgen Vestbo who continues to struggle to get me to express complex ideas simply. To these and my many other friends, thank you.

Three other groups deserve special mention. I am very grateful for the help given in the preparation of this thesis by my secretaries Joan Harper and Chantelle Murphy. Any factual errors and typographical mistakes are mine, not theirs. None of this would have been possible without the selfless generosity of countless patients suffering from COPD. They have cheerfully given their time to undergo complex and sometimes uncomfortable procedures knowing that others would benefit from the knowledge they generated. I remain enormously in their debt and hope that the results justify their efforts.

Finally I owe my greatest debt to my family. My parents long ago sent me out on a journey they knew they could not follow but always remained supportive and proud of what I had done. My sons Adam, Jim, Bob and Tom grew up uncomplainingly sharing their father's time with his all consuming job. Without them and the stoical support of my wonderful wife Maggie I would never have engaged in this work or accomplished what I have. This thesis is dedicated, with love, to them.

CONTENTS

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is now the preferred term for a range of conditions formerly called among other things, chronic bronchitis, emphysema, chronic bronchitis and emphysema, chronic airflow limitation and chronic obstructive lung disease. Defining terminology in this condition has always been a vexatious task which still provokes controversy. Although acceptable definitions exist for individual components of COPD many physicians and investigators still hanker after the relative certainty offered by Burrows et al [(1)] who identified clinical, physiological and potential pathological subgroups of what we now define as COPD. This urge to define discrete phenotypes continues[(2)] and data in this thesis have contributed to our current approaches to doing so. The recognition that simple clinically defined characteristics did not predict disease progression led to the inclusion of persistent airflow obstruction ($FEV_1/FVC < 0.7$) in the definition of COPD although whether this is the most appropriate threshold is the subject of heated debate.

The studies reported here began at a time when objective measurements such as spirometry and even the measurement of arterial gas tensions in sick patients were viewed with suspicion by clinicians while treatment was restricted to advice about smoking cessation, regular oral xanthine derivatives and, in a minority of cases, inhaled non-selective adrenergic drugs on a largely as needed basis. Exacerbations were managed with antibiotics and controlled oxygen plus intravenous aminophylline if the patient was hospitalised. There were few clinical trials to support these treatment choices and when larger clinical trials were conducted the focus was on the ability to improve FEV_1 over 3 months of treatment. Through an accident of fate and a prior enthusiasm for respiratory medicine I found myself working for the late Prof David Flenley on the MRC trial of long term domiciliary oxygen therapy in hypoxaemic COPD patients, a project which I subsequently

helped write up[3]. Prof Flenley's firm belief that clinical medicine should be related to objective measurement and that this would allow the formulation of testable hypotheses of potential benefit to patients has had a lasting effect on me. As a result I have spent much of the subsequent three decades trying to define the physiological basis of COPD, the limitations and potential value of objective testing in classifying patients and in establishing clear evidence for the role (or lack of it) of proposed treatments in disease management. The success and failures that followed from this work, together with some observations on the pitfalls of clinical trials in a chronic condition like COPD, form the basis of this thesis.

The thesis is grouped by theme rather than chronologically, in part because the work presented was conducted in parallel with studies in other areas but also because the focus of activity, particularly the clinical trials I developed and led, varied over time. Data about assessments and exacerbations began to merge in parallel with the clinical studies in an iterative process, observations in one area feeding into thinking in another. For this reason, and to anchor what follows, the original publications begin with the Executive Summary of the Global initiative in Obstructive Lung Disease (GOLD) updated in 2007 which I helped to found and where I wrote the section on the management of stable disease together with a review from 2003 of emerging ideas in COPD which is still relevant, although superseded in places by newer data. The work presented does not represent all those in which I have contributed to this field and some of these other papers are referenced in the explanatory narrative below. The selection here was based on those manuscripts which contributed most to the field when published and where I played a substantial role in the development, analysis and writing of the data. Clearly much of this work relies on the collaborative efforts of many co-workers in my own research group and in the steering committees of the large multicentre clinical trials from which I have learned so much.

After a general review the thesis focuses on papers which have improved our understanding of COPD symptoms especially as these relate to exercise capacity and also considers which physiological tests define clinically useful patient subgroups. The topic of COPD

exacerbations merits specific attention, both for its importance to patients and as a clinical trial outcome measure. The next section addresses studies which have created an evidence-base for therapy, many of which also affected our understanding of the biological behaviour of this disease. Finally a brief section updates the information presented in the light of subsequent by our group and others.

BACKGROUND

COPD has been defined by GOLD as a common and treatable condition characterised by progressive airflow limitation which is not fully reversible and results from an enhanced inflammatory response to noxious inhaled particles and gases. Exacerbations and co-morbidities are commonly seen. This formulation represents the latest refinement of the definition which has evolved since the first GOLD document was published in 2001[4]. It is currently available online and is also the first version that I have not contributed to directly since I helped found this group. GOLD has proven to be an important catalyst to research in the COPD field[5] but was always primarily directed to clinicians seeking advice on patient management. The most recent published version is presented in paper A. As evidence has accumulated, the initial recommendations have changed. Thus the early proposal for a GOLD stage 0, a symptomatic pre-obstructive phase of the disease, was withdrawn in the 2007 version as it was not really sensitive or specific enough to apply to clinical practice. Nonetheless there are data to suggest that symptomatic patients with airflow obstruction and minimal spirometric abnormality do show faster loss of FEV_1 over time[6] so the concept of early identification and intervention may yet be revisited. Until very recently treatment was introduced in the GOLD scheme in a staged manner linked to the post-bronchodilator FEV_1. As data in this thesis has shown this is not an optimal approach and would deny helpful therapy to groups of patients who might otherwise benefit. The reasons for the lack of association of FEV_1 and treatment response are one of the topics considered in the review

by Calverley and Walker[7] which gives an insight into the concepts current in the COPD field in the early part of the last decade.

A major advantage of the GOLD scheme for classifying the severity of spirometric impairment was that it provided a framework for expressing data in large epidemiological studies. The Burden of Obstructive Lung Disease study used this approach to demonstrate both wide geographic variation in the prevalence of COPD but also significant under-estimation of the magnitude of this problem in both developed and developing economies[8], a finding confirmed in Latin America by the PLATINO group[9]. This points to a diversity of causes for COPD and there are abundant data to support this idea. Tobacco exposure remains the dominant factor worldwide but contrary to earlier European perceptions this is not the only cause of COPD. Exposure to biomass fuels especially wood smoke contributes to airflow obstruction in many rural communities[10] as does prior tuberculosis[11]. Occupational factors such as organic dust exposure and welding are important but unquantified risks[12] while low birth weight and childhood respiratory disease all play a role[13]. Often several factors interact and this is the proposed explanation of the high levels of COPD seen in areas like Cape Town in South Africa.

There is familial aggregation of COPD cases[14] pointing to a genetic factor(s) in the aetiology. Alpha -1-antitrypsin deficiency is the best known and understood genetic risk factor leading to predominantly lower lobe emphysema in patients with modest or even absent tobacco exposure. The mechanisms underlying this have now been elucidated[15] and replacement therapy is available in the US. Being heterozygous for this gene may confirm a modest increase of risk of COPD[16] but other genetic variants, especially those associated with polymorphisms of the alpha-nicotinic acid receptor gene and of hedgehog interacting protein, have been consistently identified in large COPD populations[17]. Candidate gene and gene-wide association studies point to variation in oxidant –related genes and in those coding for matrix metalloproteinases as key factors favouring the development of COPD and doubtless many more targets will be identified. The complexity of

these analyses and the potential for gene-gene interaction make this a challenging area of study.

Mechanistically there is now some general agreement about the major processes involved, although not about the sequence in which they operate and interact. Persistent inflammation in all compartments of the lung has been observed with an early predominance of monocytic cells and an increase in neutrophil transit to the airway lumen in more advance disease. This form of inflammation is not controlled by even high doses of corticosteroids and a specific abnormality of histone deacetylase 2 activation has been proposed to explain this[18]. Oxidative stress is a key process promoting inflammation and accelerating lung ageing an idea supported by recent studies of telomere length in COPD and tobacco exposed animals[19]. Emphysema seems to be driven by accelerated apoptosis of alveolar wall cells, although how this relates to the enhanced numbers of inflammatory cells observed in the remaining tissue or the studies suggesting a vascular origin for this process is yet to be resolved.

The interaction between these destructive processes and the normal repair mechanisms lung tissue are also complex. We do not know whether the processes leading to it are the same in all cases, whether there is a dose response relationship with the initiating insult or indeed if damage begins at a critical threshold after which other mechanisms lead to disease progression. The hope of identifying a single critical pathway appears to be a forlorn one and considering these processes as a dynamic network with multiple interactions at both the cellular and tissue levels[20] offers the best chance of translating laboratory insights into progress at a functional level. The terminal bronchiole has been identified as the site of the earliest damage which can progress to established small airways disease and/or centriacinar emphysema[21]. Further data about how such a process evolves would be a major advance conceptually

The lag between the onset of lung damage and the time when symptoms become apparent or even until detectable spirometric abnormality appears remains a long one. The assumption that all individuals progress at the same rate throughout the disease is unlikely to be correct. This idea was driven by a simplified interpretation of the early data from Fletcher and Peto[22] showing that the group mean FEV_1 fell progressively over time irrespective of the presence of bronchitic symptoms. This concept has shaped our present understanding and definition of COPD but as is clear from reading the original substantive publication, not all subjects showed this pattern of loss in lung function. Studies which have attempted to modify the rate of FEV_1 decline are discussed in detail later but this outcome is clearly a complex one. Although apparently healthy smokers show a decline in FEV_1 that is modified when they stop smoking[23], only 40% of patients with established COPD (GOLD 2-4) are rapid decliners (greater than 40ml per year) with 30% showing no decline or even improvement in lung function over this period[24]. Hence some individuals present with COPD sooner than others, perhaps because they experience more exacerbations contributing to their lung damage.

The focus of physiological abnormality has moved from seeing COPD as a disease primarily of airflow obstruction to one where changes in lung volume secondary to this obstruction are seen as the primary problem. Thus the FEV_1/FVC defines a threshold for considering COPD but the clinical severity thereafter depends on the impact on operating lung volumes. Loss of elastic recoil secondary to emphysema together with thickening and fibrosis of the wall of the small airways increases the closing capacity of the lung and eventually residual volume rises, with a consequent reduction enforced vital capacity. Subsequently end expiratory lung volume becomes dynamically regulated at rest and during exercise when patients hyper-inflate dynamically rather than decreasing their end expiratory lung volume[25]. The resulting hyperinflation compromises the ability of the respiratory muscles to generate force and produces changes in chest wall volume which can further add to the overall work of breathing and are discussed later. Ultimately the matching of ventilation and perfusion is

compromised and the arterial oxygen tension falls initially during exercise and subsequently at rest. Depending upon the mechanical burden on the lungs, arterial C02 tension rises and patients with sustained hypoxaemia and hypercapnea develop secondary maladaptive changes which further compromise their clinical wellbeing. In most but not all patients, the natural history of disease is punctuated by intermittent exacerbations of symptoms which impair the individual's health for long periods[26] and which are now the focus of significant research efforts described below.

Recently there has been renewed focus on the presence of co-morbid conditions which occur in COPD more frequently than would be predicted from exposure to known risk factors. Lung cancer and pneumonia are both common in COPD[27;28] and their presence may reflect persistent pulmonary inflammation. Depression[29], metabolic syndrome, diabetes, osteoporosis and gastrointestinal reflux[30;31] are all significantly associated with COPD. Cardiovascular disease is one of the commonest associations[32] and there is a clear relationship between an abnormal pulse-wave velocity and the presence of CT-defined emphysema[33]. Possible explanations for this include over-spilling of inflammatory mediators from within the lungs or a shared common previous disposition, either genetic or acquired, to organ damage in people with COPD.

The remaining parts of this thesis offer a brief general review of the importance and context of the papers presented.

ASSESSING THE STABLE COPD PATIENT

As outlined in the GOLD summary document (A) a clinical diagnosis of COPD requires a combination of symptoms and/or appropriate risk factors, together with spirometrically defined airflow obstruction, ideally recorded after a bronchodilator. The typical symptoms and signs associated with COPD have been reviewed in detail[34] but there is general agreement that cough, with or without the production of small amounts of initially mucoid sputum is the earliest feature. This may be persistent and meet the epidemiological criteria

for chronic bronchitis (3 months for 2 consecutive years) although the importance of this definition remains unclear as many people with bronchitic symptoms do not have airflow obstruction. Nonetheless, identifying patients with a bronchitic history does select a sub-group more likely to exacerbate and therefore potentially one more responsive to treatment reference. The mechanisms underlying cough in COPD remain obscure and were initially thought to represent a normal response to local increases in mucus production[35]. A more plausible explanation has come from our studies of cough reflex in asthmatics and COPD patients [B]. We were the first to demonstrate that increased non-specific cough reflex responses to capsaicin in COPD were similar to those seen in chronic asthma. Our data suggests that persistent inflammation in the large and medium airways is likely to be a major contributor to this symptom. The poor relationship of these objective measures to subjectively reported cough highlights the difficulty in evaluating this troublesome complaint.

Although many other symptoms are reported by COPD patients, the most feared is breathlessness, either at rest or during exacerbations. Several scales are available to grade the intensity of this symptom, the most widely applied being the simple MRC dyspnoea scale which tracks quality of life well in COPD patients[36]. This scale gives an insight into the functional impact of COPD but some have argued that specific symptom qualities might be associated with particular diseases. We conducted standardised questionnaires in patients with COPD, bronchial asthma and idiopathic hyperventilation to provide a range of lung problems that might test this hypothesis. Using principal component analysis to interrogate the data, we found that whatever the disease causing the breathlessness the symptoms complained of were very similar (C). More mechanistic insights of this process, in particular the importance of reduced inspiratory reserve volume, have subsequently been published[[37] and emphasise the importance of hyperinflation and a reduced inspiratory capacity in generating this symptom in patients with lung disease.

Although COPD is defined in terms of airflow obstruction, there is substantial difference between patient's variability in symptoms such as breathlessness and problems such as

exacerbation-frequency and overall measures of quality of life which we have usually evaluated using the St George's respiratory questionnaire (SGRQ). One of the major purposes of the ECLIPSE (Evaluating COPD longitudinally In Pursuit of Surrogate Endpoints) cohort study which I helped design and manage was to understand how variable the clinical presentations of COPD were and whether they related to other objective markers which evolved over time. This study has provided important insights into the heterogeneous nature of COPD in hospital practice in the early 21st Century[38] and other papers arising from it are referred to throughout this presentation.

Although ECLIPSE endeavoured to capture information about a wide range of COPD phenotypes, all which were excluded for practical reasons were patients who were hypoxaemic with a history of clinical cor pulmonale. Such patients appear to be less frequent now than 25 years ago and this likely reflects the changing demographics of COPD and the availability of better methods of identifying impaired left ventricular function. Nonetheless, this form of COPD is still commonly seen in many developing countries and when hypoxaemia is significant, usually below 8.0 kPa, the incidence of clinically important pulmonary hypertension becomes significant. Work from the UK MRC oxygen trial which I participated in at the beginning of my research career [3] and from the US nocturnal oxygen treatment study[39] has established that long term domiciliary oxygen treatment is beneficial in such patients. COPD patients like this experience significant nocturnal oxygen desaturation[40] with associated increases in pulmonary artery pressure mainly due to physiological hypoventilation which worsens their background degree of hypoxaemia during sleep[41]. There continues to be debate about the importance of sleep quality in hypoxaemia and COPD. The study in Paper D was the first to objectively demonstrate that sleep quality was poor in COPD and might be improved by giving oxygen. This has been challenged by other subsequently but a recent met-analysis in less severe patients still found an association between sleep quality and hypoxaemia, suggesting that this may be an important factor affecting such patients [McSharry et al under-revision Respirology].

Secondary polycythaemia, defined by an increased in red cell mass rather than simply an elevated packed cell volume, is seen in residents of high altitude where the arterial pO_2 is reduced and was noted as part of the "blue and bloated" hypoxaemic COPD patients' problems. However, there was not a simple relationship between arterial $p0_2$ and red cell mass. The main factor accounting for the variability between patients proved to be the extent of cigarette smoking and particularly carboxyhaemoglobin in the blood as described in Paper E. Patients who continued to smoke did not show a fall in red cell mass when given oxygen therapy, one of the few physiological pointers confirming the benefits of smoking cessation on the immediate response to treatment in COPD. Once COPD patients had their carbon monoxide levels raised to values equivalent to that seen during cigarette smoking, there appeared to be a reduction in exercise performance, this measured by the 12 minute walking distance (F). Rather surprisingly these studies have never been repeated and given the modest number of patients studied, it would be reassuring if they had been. Possibly the advice that all patients should stop smoking for the many other valid reasons is sufficient in itself not to challenge these observations. Despite the relatively simple methodology, we have been able to show important short term improvements in exercise, performance and symptoms in a similar number of patients studied with a 6 minute walking test after bronchodilator treatment and oxygen[42].

The assessment of COPD has proven controversial. Routine assessments of lung volumes helps to characterise the patient but tends to be confined to specialist centres and provides an overall impression of physiological disturbance rather than suggesting specific interventions. For many years there has been enthusiasm for using the spirometric response to short-acting inhaled bronchodilators to establish the 'reversibility' of the disease to treatment and, by extrapolation, identify which patients will not get better. This approach proved to be wrong, although my group initially promoted the idea and subsequently have spent much time trying to correct the misconceptions to which we inadvertently contributed. Our first aim was to establish in an unselected group of COPD patients how often

reversibility was seen[43] and to determine whether corticosteroid treatment improved lung function in COPD. These results appeared to separate responders using the widely adopted criteria of a percentage improvement from baseline and we found that those showing this improvement were more likely to show increases in FEV_1 after 2 weeks of oral corticosteroids. At this time routine treatment for COPD did not include inhaled corticosteroids and so we studied a relatively treatment naive population. As a result many people accepted the value of bronchodilator testing in COPD, it was recommended as part of routine assessment by the British Thoracic Society and ultimately became incorporated in the Quality Outcomes Framework for payment of General Practitioners in England.

Unfortunately our data had been taken beyond its original purpose. Subsequent studies particularly those we embedded in the Inhaled Steroids in Obstructive Lung DiseasE (ISOLDE) study, showed that irrespective of the criteria used to define reversibility or the dose of drug used to induce it, there was substantial day to day variation in patient classification and using the initial response to two bronchodilator drugs did not identify patients with different clinical outcomes [G]. These findings were confirmed in the UPLIFT study population[44] where a decrease in the absolute FEV_1 increase in more severe disease accounted for the less frequent occurrence of reversibility in GOLD stage IV. We have confirmed this in our ECLIPSE cohort which showed similar degrees of absolute spirometric change post-salbutamol in a GOLD stage II patients and healthy smokers. The measures of reversibility chosen are very sensitive to spontaneous, possibly physiological, fluctuations in pre-test FEV_1, a finding in both ISOLDE and ECLIPSE. Whether there is value in classifying large groups of patients by their 'average' reversibility status remains unclear. There was some evidence to support this as less reversible patients showed a slower decliners in FEV_1 in ECLIPSE[24] but even in such well characterised patients it is hard to exclude the confounding effect of baseline FEV_1 entirely. Studies of the spirometric response to oral corticosteroid in ISOLDE failed to identify a responsive asthmatic subgroup or indeed any

relationship with subsequent clinical progress[45]. As a result of these data reversibility testing is no longer recommended for the routine assessment of COPD patients.

Identifying the best measure of response to treatment has been the topic of several of our studies. Approximately 23% of COPD patients show a greater improvement in FVC than FEV_1 after a bronchodilator and this is particularly likely if they have emphysema or a low pre-test FEV_1[46].However FVC is a relatively effort-dependent test. Inspiratory capacity (IC) has a better between test reproducibility than FVC[47] and we found IC to be more responsive to high dose bronchodilators in severe COPD patients than was FEV_1 [H]. This improvement in lung volume was accompanied by changes in breathing pattern that favoured better lung emptying. We did not see any change in the number of patients showing expiratory flow limitation (EFL) during tidal breathing as identified by the negative expiratory pressure test (NEP). EFL is an important determinant of dynamic hyperinflation and impaired exercise capacity in COPD[48]. Testing using the NEP method is relatively complex and can only sample a limited number of breaths. Working with colleagues from the Politecnico di Milano we developed a non-invasive method based on measurements of forced oscillatory mechanics to establish whether a breath was flow limited [I]. This proved to be very reliable when related to the 'gold standard' of invasive balloon catheterisation and could be applied to multiple breaths therefore allowing an estimate of the patient's degree of tidal EFL. This approach involved an analysis of each breath by its behaviour drug inspiration and expiration. Previous studies using a related measurement of mechanics by the impulse oscillation algorithm found that there was little change in measured resistance after bronchodilator drug[[49]. Using within breath analysis and allowing for the effects of tidal EFL we could demonstrate much larger effects of bronchodilators at rest on COPD than had been seen with alternative methods [J]. Studies re-analysing the ECLIPSE data are now underway in the hope of better defining a physiological phenotype based on the presence of EFL at rest.

As impairment of exercise capacity is one of the commonest findings in COPD it was reasonable to consider whether this was a useful outcome measure to assess the effect of treatment. One of the first studies to use self-paced walking tests as an outcome in COPD research was our examination of the effects of oxitropium bromide, an anticholinergic drug, in 24 patients with stable COPD [K]. Not only did we see a positive effect on lung function and exercise performance, a finding we and others have confirmed with other drugs in this class[50], but this as the first occasion when we demonstrated that improvements in exercise capacity were unrelated to the degree of change in FEV_1. Subsequently a compelling body of evidence has been presented for the central role of changes in operating lung volume as reflected by reductions in IC during exercise as a central mechanism in exercise limitation in COPD[51]. We hypothesised that the adaptive response of the chest wall to these volume changes might vary and explain some of the apparent discrepancies between lung function and exercise capacity which have been frequently noted in COPD[52]. Working with another group of colleagues in Milan who developed a non-invasive method to measure chest wall volume during exercise (optoelectronic plethysmography OEP), we undertook an observational study of stable COPD patients recording how they partitioned any volume change in the chest wall between the ribcage and abdominal compartments. Although most patients showed the expected hyperinflation in the chest wall during exercise a minority tried to retain the normal breathing pattern of decreasing operating volumes below the resting end-expiratory volume as exercise began. In the face of fixed EFL this was a poor choice and these euvolumic patients had a worse exercise performance than did the hyperinflators [L]. This behaviour is associated with thoracic gas compression and blood shifts away from the central circulation, changes seen in all more severe patients including those who hyperinflate their chest wall. The resultant reduction in oxygen delivery to exercising limb skeletal muscle and impairment of diaphragm perfusion contribute significantly to exercise impairment[53]. We extended our observations to look at whether changes in the behaviour of the chest wall explained the variability in the response to bronchodilators noted in study K. This proved to be the case as we saw that while almost all subjects improved tests of

expiratory flow and decreased their operating lung volume after Salbutamol, a minority had worse exercise performance because they changed their breathing pattern from a hyperinflating to a euvolumic response[54]. This suggests that some of the ways that we cope with changes in lung mechanics may be learned behaviours and that acute testing may lead clinicians to incorrect conclusions about the benefits of treatment.

Clinical observations have long suggested that COPD patients may show paradoxical in-drawing of their lower ribcage during inspiration and that these patients are more breathless than others with similar spirometric abnormaility. We applied our OEP methodology to test this idea objectively. Using an appropriate age-matched control group to determine the normal chest wall behaviour in healthy older subjects we established values for the presence of rib cage paradox, demonstrated that when present it persisted during upright exercise and was associated with a pattern of early onset of dynamic chest wall inflation during exercise [M]. These patients were more likely to be limited by breathlessness thereby providing a physiological rationale for a longstanding clinical observation.

Perhaps the most important insight into exercise testing in COPD has come from the belated realisation that an improvement in exercise capacity is not the same as an improvement in daily activity[55]. The reasons why this should be so are now being studied but observations from study K may be relevant. In this and indeed all subsequent studies where the patient could select the difference walked there is an individual variation in the degree to which patients report improved dyspnoea at the end of exercise. Some will walk to the same distance for less dyspnoea while others walk to the same symptom intensity but cover a greater distance. Moreover these are tests conducted on the level not an incline as applies to stairs where other factors like fatigue in exercising muscles with a compromised blood supply may be more important. Future studies will have to look at these more challenging endpoints if patient well being is to be improved more effectively.

EXACERBATIONS

Although long recognised by patients as clinically significant episodes[] it was only in the mid-1990's that exacerbation rate was included as a secondary endpoint in a major clinical trial, the ISOLDE study which I developed together with Professor Sherwood Burge. Although there were attractions in looking at a symptom-based endpoint as used in the antibiotic trial of Anthonisen[56] and the comprehensive data arising from the London group led by Prof Wedzicha[57] at the time of ISOLDE analysing and interpreting symptom data in a large number of participants over a long period of follow up was technically daunting. Operationally we defined significant exacerbations as those requiring treatment with antibiotic and/or oral corticosteroids with severe episodes being those leading to hospitalisation or death. A subsequent consensus conference in which I participated supported this approach[58]. Our data from ISOLDE showed that health status, both generic and disease specific were impaired in COPD[59] and that both the baseline health status and the rate at which it deteriorated over time were related to the number of exacerbations reported by the patient[60].However deciding when exactly an exacerbation had occurred and hence who might benefit from treatment proved more complex than we first thought.

In a post-hoc analysis of the ISOLDE data we found that treatment with inhaled corticosteroids decreased the frequency of exacerbations in patients with an FEV_1 <50% predicted [N], a value which subsequently became accepted as a treatment threshold. In fact as the paper shows had a different metric (number of patients with >1 event per year) been used then the apparent effect of the FEV_1 level was lost. These equivocal findings should have alerted us to the dangers of interpreting exacerbation numbers in a clinical trial. When symptom diary cards were used to determine the presence of an exacerbation the effect of treatment with bronchodilators and corticosteroids were supported but there was discordance between events identified by symptoms and those recorded as a health care use event [O].

Health care utilisation events were less common but more economically important and so remain the primary outcome of clinical studies. However, exacerbations are not normally distributed in time and are now known to exhibit clustering[61]. As a result, summary statistics in clinical trials can be misleading as shown in a series of articles by Suissa[62] and ourselves which led to the analysis published by Keene et al[63]. As a result, when expressing event rates we now apply appropriate statistical methods.

Our knowledge of exacerbations has grown rapidly in the last decade. In a post hoc analysis of data from the TORCH (TOwards a Revolution in COPD Health) data, the largest exacerbation data set reported so far, we identified a range of predictive factors including baseline lung function, severity of breathlessness, prior history and body mass index. A further major factor we noted was seasonal variation which tracked temperature changes in both the Northern and Southern hemispheres (P). Exacerbation rate in the tropical climate showed little variation over the year, although whether this reflected the smaller contribution of centres in this area or a different driving factor such as changes in local pollution[64] remains unclear. Using the large observational data set from the ECLIPSE study, we established that 70% of patients have a stable pattern of exacerbations over time, either tending to exacerbate frequently or not at all (Q). The prior history of exacerbations was the dominant predictor of the likelihood of recurrence, although lung function health status and a history of gastro oesophageal reflux were also important. This study is the clearest demonstration that baseline lung function does not preclude either being a frequent exacerbator or even being hospitalised as a result and this has had implications for our approach to clinical management.

Defining the changes in lung mechanics that accompany exacerbation had largely been confined to ventilated patients in intensive care units. We were the first to report detailed studies of lung mechanics in non-ventilated but hospitalised COPD patients (R). We found that changes in spirometry after admission minimal over the first 3 days while changes in inspiratory capacity were larger, could be detected almost immediately after administration of

a bronchodilator and track changes in patient-reported breathlessness. Respiratory system reactance measures were equally sensitive and offer the potential of a non-volitional marker to monitor the progress of exacerbations. Non-invasive ventilation has been a highly effective life-saving treatment in the management of respiratory acidosis secondary to hypercapnoea in COPD exacerbations[65]. However, not all patients benefit and identifying those at risk of NIV failure is important when planning management. In paper S, we established that tachypnea and hyperglycaemia on admission independently predicted those patients with a poor clinical outcome with some modest improvement in predictive power when these simple clinical measurements were combined. These markers of lung function and systemic response were better than previously recommended indices such as severity of hypercapnea or acidosis when stratifying risk. Further work exploring these simple end points appears merited.

Treatment of acute exacerbations has changed little over the course of this thesis, although the principles of controlled oxygen are still not always appreciated by emergency room staff[66]. Antibiotics and bronchodilator drugs form the mainstays of management but for many years there was uncertainty about the relative merits of supplementary aminophylline and routine oral corticosteroids in the management of exacerbations. Two studies from our group have resolved this. In one, patients admitted with uncomplicated exacerbations of COPD were randomised to intravenous aminophylline or placebo in a double blind fashion[67]. There were no differences in clinical outcome, save for a clinically inconsequential reduction in arterial C02 tension in the aminophylline group. Given the toxicity and lack of effect of this therapy, it should not be used. The second study (T) was published almost the same time as a multi-centre veteran study from the USA which drew similar conclusions[68]. We randomised patients to either a course of 30mg of Prednisolone for 10 days on admission or an identical placebo. We found that those treated with the oral corticosteroid showed a more rapid improvement in FEV_1, a shorter hospital stay but slightly higher blood sugar values during the recovery phase. The magnitude of improvement we

saw was similar to that seen in the US study which used much higher doses of corticosteroids. Our data suggests that a shorter treatment period might be equally beneficial but this has not been rigorously explored and is an area that needs investigation. Our group also contributed to the move towards managing uncomplicated exacerbations of COPD in the community. In one of the key randomised clinical trials, we showed that it was both safe and acceptable to discharge patients from Accident & Emergency with support who would otherwise have been hospitalised[(69)], a finding supported by other UK studies[(70)]. Although changing the place of care has advantages for patients and potentially offers cost saving, it does not diminish the impact of exacerbations themselves, nor decrease their number, which remains an important goal in future management plans.

TREATMENT OF STABLE COPD

As noted earlier the treatment options open to COPD 30 years ago were very limited. The MRC trial of domiciliary oxygen treatment, which I contributed to and helped author, was one of the first studies to consider physiologically rational treatment in patients defined as having COPD by spirometry. It achieved its goal of showing mortality difference between groups and could now never be repeated for ethical reasons, which is perhaps as well as the intervening years have seen an almost exponential rise in the complexity, regulation and monitoring of clinical trials which has begun to limit their value as a tool to define routine clinical practice. The substantial expense associated with this means that only pharmaceutical companies have the resources to support investigations which produce immediate changes in management, and inevitably this has meant that most studies have looked at pharmacological solutions rather than examining the even more challenging area of integrated care. Sadly the Medical Research Council has not funded a major clinical study in COPD since the oxygen study of 1980's. Despite this we now have a much larger evidence base on which to make clinical decisions and the main lessons which we have learned, both from the outcomes of the studies and the process of doing them which is summarised in a review published in 2007[(71)] which predated the UPLIFT trial[(72)] about which

I have made further editorial comment[73]. The heterogeneity of COPD which has already been discussed means that large numbers of patients have to be studied for relatively long periods of time if a generalisable conclusion is to be drawn from any treatment intervention. Indeed looking at clinically important outcomes such as exacerbation rate, and even more so when considering mortality, which is happily a relatively infrequent event, means that substantial resources have to be committed to undertake an adequately powered study. A further less appreciated methodological problem has been the impact of including a placebo group when studying a drug broadly within the class of one which has been used off label to manage the disease already. This often means changing the patient's medication at the outset of the study, if the therapy is effective then the patients often become clinically less stable and the patients treated with placebo are more likely to experience adverse events and withdrawal from follow-up, leaving a 'healthy survivor' population among the placebo treated patients. This problem was first described in paper U where patients who withdrew from the placebo group had a worse health status and lung function, and showed a more rapid deterioration in their clinical state over time than those who did not. As the same was not true for those on the active treatment it was clear that the populations being compared at the end of the study were not really the same. Similar findings are seen in other studies and the sources of clinical bias are now well recognised by those in the field[74], but much less appreciated by others who simply pool the data to estimate outcomes.

One of the major treatment changes of the last two decades is the development of long-acting inhaled bronchodilators with relatively low side effect profiles. The data in paper V was the first to show that the long-acting antimuscarinic drug tiotropium had a truly 24 hour action, irrespective of its time of dosing and this was present after repeated treatments. Of greater interest scientifically was the fact that this drug, which should have abolished the action of cholinergic innervation on the airway smooth muscle, did not change the nocturnal fall in lung function. The magnitude of this diurnal variation in airway calibre was similar in the COPD patients who start from a lower baseline function, to that seen in health[75]. These

data provide further evidence that the airways move muscle is not abnormal in COPD and the problems relate to changes in lung structure which produce the fixed airflow obstruction.

A second major theme has been to determine whether anti-inflammatory therapy, a rational treatment for a disease associated with persistent pulmonary inflammation[76], has a clinical role either as a monotherapy or in combination with another agent such as a long-acting beta agonist. Initial reports of monotherapy with inhaled corticosteroids appeared to be very encouraging[77] but there were concerns that the population study included many who would be classed as having bronchial asthma rather than COPD. The large EUROSCOP study in patients with COPD who continued to smoke [78] and the smaller Copenhagen City Lung Study in patients with much milder disease[79], both failed to show any effect of inhaled corticosteroids on the rate of decline of lung function, the most commonly used index of disease progression. Individuals identified in these studies were largely drawn from population studies or from volunteer investigations of patients who wished to stop smoking but could not. Together with Professor Burge in Birmingham I developed a protocol subsequently led the ISOLDE study which compared 1000mcg of Fluticasone Propionate inhaled daily over three years and an identical placebo in patients with significant COPD, predominantly gold stages three and four (W). Again the primary outcome was the rate of change in FEV_1, and this was not modified by these drugs. However, as noted previously data about the improvement in health status[59] and reduction in exacerbation rate [N] with treatment did impact clinical practice but were not sufficient to lead to widespread licensing of inhaled corticosteroids for this purpose.

The TRISTAN study described in paper X involved twice the number of patients as in ISOLDE, but the study period was for one year. This was a four armed double blind placebo controlled parallel group trial comparing fluticasone propionate, the long-acting beta agonist salmeterol, the combination of the two drugs and placebo, all delivered in single inhalers, to COPD patients with a history of prior exacerbations. Again there was evidence of differential drop out with more people withdrawing from the placebo arm than from the active limbs of

the study, meaning that estimates of the effects size, particularly in clinical variables, were conservative. All the active treatments were associated with improvements in lung function which seemed to be a more sensitive way of distinguishing between them, reflecting some of the issues of statistical power already discussed. Moreover there was evidence of a significant improvement in health status in those patients receiving placebo which made it hard to achieve the minimally clinically important change in the active treatment groups, even though all active treatments were statistically significantly better than placebo for this outcome. More evidence of the benefits of inhaled steroids and long-acting bronchodilator combination treatment came from another study (Y) which compared budesonide and formoterol as the inhaled steroid and LABA drugs. In this study we tried to overcome the problems with variable health status by optimising clinical management with a period of oral corticosteroid treatment, as used in the ISOLDE study, and also regular long-acting bronchodilators before the randomisation. The effects on health status were much more dramatic here and the patients included were sicker and had more exacerbations than was seen in the TRISTAN study. The effect of treatment with a combination inhaler was also more clear cut, although interestingly the inhaled steroid alone reduced the number of exacerbations treated with oral corticosteroids, a finding which seems to be the hallmark of all anti-inflammatory therapies in COPD.

By far the largest and most ambitious study of this type was the TORCH study which I designed and led (Z). Here the aim was not just to see if treatment modified health status or exacerbations, but whether regular treatment with a long-acting beta agonist - inhaled corticosteroid combination, could reduce mortality. In such a large study we also had much more power to identify less frequent adverse events than was the case in any of the previous trials. We studied over 6000 patients in multiple centres around the world, with approximately 1500 in each limb of the study. These numbers were based on the estimates mortality derived from pooling previous studies of inhaled corticosteroids[80], and in retrospect were probably too optimistic given the steady improvement in mortality over time

since patients were recruited into these earlier trials. The patients were followed on an intention to treat basis over three years in this four arm study which mirrored the design of the TRISTAN trial. We were the first pulmonary study to develop an independent clinical end points committee whose approach to classifying causes of death has been published[81]. The study also incorporated specific measures of bone mineral density and eye examinations to evaluate the risk of osteoporosis and cataracts in patients with COPD taking inhaled corticosteroids. We found that the mortality of patients randomised simply to short acting bronchodilators and/or theophylline treatment was lower than we had anticipated, with 15% dying over the three year study compared to our estimate of 18%. This not only reflected changes in overall disease management but the fact that many patients who withdrew from the trial then went on to take one of the active treatment arms in an open label fashion, but by the rules of the intention to treat analysis were still considered as belonging to the placebo group. Moreover the operation of the data and safety monitoring committee meant that the timing of the second analysis compromised the statistical ability of the study to show a difference. Frustratingly, despite all these problems the difference between active and placebo treatment approached significance very closely with a p value of 0.052. As we had set our p value at 0.05 at the outset of the study, we had to concede that we had not shown a conclusive benefit, although the assertion made by some that there was no evidence for the mortality effect appeared to us to err in the opposite direction.

The abundant statistical power for other secondary end points did allow us to conclusively establish that combination treatment was more likely to reduce exacerbation rates and improve health status than placebo or the individual components. In a pre-planned analysis conducted after the main results were published we found that all the active treatments reduced but did not abolish the accelerated decline of lung function which had been the primary goal in other clinical trials AA. Why this happened is not immediately apparent but a reduction in exacerbation frequency is a plausible candidate mechanism. Once again the importance of studying large patient numbers is clear. This effect on lung function decline of

any active treatment may explain why tiotropium in the UPLIFT trial failed to modify lung function decline in all except the treatment naive patients. The final major trial in this sequence studying beta agonists and inhaled corticosteroids was the INSPIRE study in which a combination of long-acting beta agonist and inhaled steroid was compared with tiotropium monotherapy over a two year study in patients with a history of exacerbations[82]. We did not see not see any difference in exacerbation rate, although intriguingly there were significantly fewer exacerbations treated with oral corticosteroids in the combination arm, and conversely more treated with antibiotics than was the case with tiotropium. Once more we used a run-in period with oral corticosteroids, and this did seem to simplify the interpretation of the health status data which were better on the combination treatment. Rather surprisingly more patients withdrew on tiotropium than on combination, and again this compromised the ability of the study to give us clear cut an answer on the exacerbation issue as we had hoped.

Other approaches to anti-inflammatory treatment have been developed but most of these failed to either be effective or tolerable in man. An exception has been the use of phosphodiesterase IV inhibitors which exploit the wide distribution of this enzyme within tissues to modify inflammation. Even here the majority of compounds have failed to progress but one of them, roflumilast, has now undergone extensive clinical studies, many of which I designed and directed. After a six month dose ranging study in COPD[83] we studied 500mcg roflumilast or placebo in patients with GOLD stage 3/4 disease without necessarily having an exacerbation history over a one year period. These data were disappointingly negative[84]. We saw small improvements in post-bronchodilator FEV_1 which was statistically significant, but of themselves probably clinically unimportant. We did not see any difference in the exacerbation rate but this was significantly lower than we had anticipated from earlier studies with inhaled corticosteroids. There was evidence for a reduction in the number of episodes treated with oral corticosteroids, and also positive impacts in patients with more severe disease and in those with chronic bronchitis. When the data from this study were

pooled with an identical but currently unpublished US trial, we were able to identify a potentially responsive patient sub-group[85]. This led to the construction of two replicate studies of this post-hoc-defined population to confirm that the apparent effects seen initially were present. The results of this clinical trial are described in paper BB where all patients had a history of chronic bronchitis and prior exacerbations before receiving treatment. Our original sub-group findings were confirmed in both studies with a significant reduction in exacerbation rate amounting to around 20% of the baseline value. This was present irrespective of the use of background inhaled bronchodilator treatment[86]. As an oral therapy roflumilast had more adverse events particularly pharmacologically predictable diarrhoea, nausea and headache. These were generally self-limiting, but roflumilast treatment was associated with weight loss irrespective of the presence of these other symptoms. This appeared beneficial in the most obese sub-group and largely consisted of fat mass decreasing, but the use of this drug in patients who are already underweight must be viewed with caution. A further large study is underway to determine the beneficial effects, or otherwise, of roflumilast on top of maximal treatment with existing bronchodilators and inhaled corticosteroids.

Not all treatments for symptomatic COPD need be pharmacological. Increasing the concentration of inspired oxygen during exercise can improve six minute walking distance and reduce breathlessness, although these effects are most evident in severe COPD and supplement the similar actions seen after an acute bronchodilator[42]. Oxygen administered by tight face mask can increase endurance shuttle walking time in normoxemic COPD. Reducing the gas density with heliox, which permits better lung emptying at high expiratory flows can further increased shuttle walking distance as shown in paper CC. In this adequately powered study the combination of increased oxygen concentration and helium produced dramatic improvements in exercise performance, particularly in patients with low baseline FEV_1. Unfortunately the limitations to the supply of helium and the need for tighter fitting face masks still limit the general application of this promising and potentially dramatic

treatment. Many patients, particularly in the UK, use oxygen to decrease breathlessness either acutely during an exacerbation, or most commonly after exercise, an approach advocated in earlier studies of this treatment[87]. A careful clinical and physiological study by Stevenson presented in paper DD acute administration of oxygen by face mask after a standardised exercise stimulus did not influence the rate at which breathlessness resolved or its severity, whether the oxygen was administered through a mouth piece or a face mask. There is clearly a significant placebo effect here, although there may be some effects from cooling of the face which reduces the sensation of breathlessness. Given the expense and inconvenience of having oxygen in the home we should focus on better patient education rather than offering cylinders or concentrators in what appears to be an expensive placebo.

One of the major non-drug therapies is pulmonary rehabilitation which is very effective in improving exercise capacity and health status, at least in those ho complete the individualised programme without experiencing an exacerbation[88]. These effects are larger and more noticeable to the patient than those seen with drug treatment but their magnitude declines over time to values similar to those not undergoing rehabilitation. We confirmed that significant improvement was possible after rehabilitation but although the capacity to perform walking exercise increased this did not necessarily translate into more daily activity at home (EE). The greatest change in daily activity occurred in patients with less severe airflow obstruction highlighting the need to understand the individual patient's problems when prescribing any therapy.

TREATMENT SAFETY

In general the drugs used to treat COPD are very safe and produce much less in the way of side effects than agents employed in the 1960's and 70's reflecting the low absolute doses delivered to the airways. Despite this there have been concerns about the risks of treatment in COPD patients, which is understandable given the multiple co-morbidities which accompany this disease. The problems associated with roflumilast have already been

mentioned, but particular concerns are being raised about long-acting beta agonists and inhaled corticosteroids. Concerns about long-acting beta agonist use continue to surface in the USA where these drugs are perceived as being more dangerous than they are thought to be in Europe or the rest of the world. The reasons for this are complex, but have indirectly impacted the COPD field where one rather selective meta-analysis has proposed that LABA use is dangerous in COPD. Although this study was inaccurate it did raise concerns about the risks of treatment, and it was reassuring to see that not only was there no evidence for increased cardiovascular death rate in the TORCH study but in fact patients receiving these drugs singly or in combination with inhaled corticosteroids had a lower mortality, as shown in paper FF. If anything, the benefits of treatment were larger in patients who had more cardiovascular risk, and this has led to a very large international prospective trial to test this hypothesis in patients with moderately severe COPD. The long-time course over which some adverse events develop makes the study in clinical trials difficult, although database information is also potentially confounded by disease severity and prescribing bias. TORCH offered relatively long exposure to inhaled corticosteroids in a large number of subjects and the results where reassuring as were the data from more detailed studies of bone mineral density and cataract risk in the US sub-group[89]. Although osteoporosis and osteopaenia were common in COPD there was no relationship to prior inhaled or oral corticosteroid use. Patients receiving inhaled corticosteroids did not have an accelerated loss of bone mineral density and reported the same number of new cataracts. However there was clear evidence that treatment with regimes including fluticasone propionate was accompanied by more reports of pneumonia[90]. Not all pneumonias were confirmed by a chest X-ray but the signal was still present when the analysis was restricted to radiologically definite events. Surprisingly mortality due to pneumonia was not increased and this has subsequently been confirmed in observational studies of hospitalised patients using inhaled corticosteroids for COPD[91]. The INSPIRE trail confirmed the association of pneumonia and fluticasone propionate but had the advantage of recording symptoms daily on a diary card which allowed us to examine events in the weeks before the diagnosis of pneumonia was made.

These data are presented in paper GG which shows that similar numbers of pneumonias in the corticosteroid and tiotropium groups present after a few days of symptoms but the excess of events during corticosteroid therapy is accounted for by episodes which would count as symptomatic and/or treated events where symptoms do not resolve fully, often persisting for many days before a diagnosis of pneumonia is made. This may be a specific issue with fluticasone propionate as it was not seen when a large database of budesonide trials were reported[92]. Whatever the mechanism the effect in patients appears to be less serious than at first thought.

FUTURE DEVELOPMENTS

COPD remains a global problem that is likely to slowly decline among men in the developed economies but will increase among women and in both sexes across the developing world. The present BOLD surveys set a benchmark against which change can be assessed and will need to be repeated periodically to chart the size of this global epidemic. In the UK non-smoking COPD, whether work-related, secondary to childhood respiratory disease (especially of extreme prematurity) and to regular non-tobacco inhaled drug use, will become more important. The interaction of COPD and obesity will need to be addressed as obesity can have some protective effects on mortality and dynamic hyperinflation in COPD[93] but carries its own risk of serious co-morbidity as well as a potential for misdiagnosis spirometrically which can make it hard to know if similar severities of lung disease are being compared. A greater understanding of early disease and the importance of respiratory bronchiolitis, small airway loss and accelerated aging mechanisms[19] may allow us to separate the effects of disease progression from those of the primary mechanisms causing disease in the first place. The association of emphysema and cardiovascular disease suggests that key co-morbidities may occur in specific patient subsets and lead us to undertake CT scanning more readily than in the past Although no simple biomarker has yet

proven itself in terms of patient stratification new methods of identifying flow-limitation and recording lung mechanics noninvasively may be successfully adapted to patient care and enable effective telemonitoring to identify exacerbations at an early stage in their natural history.

Therapeutically we need to be sure that treatment is appropriate for non-smoking COPD all the studies in this thesis recruited typical current or ex-smokers. Effective smoking cessation remains a key goal and a general health care challenge. More specific approaches to vaccination perhaps by targeting innate immunity may reduce exacerbations as well as pneumonia episodes as well as decreasing lower airway colonisation. Expensive and potentially highly potent biological may decrease exacerbations through a variety of mechanisms but are only likely to be financially and clinically viable if they reduce re-hospitalisation in severe disease. A range of interesting small molecules with anti-inflammatory potential including CXCR2 and p45 MAPkinase antagonists are in development but translating these into a viable clinical endpoint remains a challenge given the late stage at which COPD presents clinically. However these drugs should be easier to test in clinical trials as they will need to be effective on top of standard therapy, at least initially.

The same, sadly, is not the case for the next generation of once daily inhaled bronchodilators and corticosteroids which multiple pharmaceutical companies, like blind men fighting over combs, are now committed to bring to market. Hopefully some of the effort going into this will generate more useful knowledge about COPD which can inform general clinical practice. Improving the care of hospitalised COPD patients may involve further technical developments in non-invasive ventilation but the major gains at present will flow from better organised and more holistic care rather than new drugs.

COPD is still defined as a progressive disease but recent data from the ECLIPSE study has challenged that paradigm. In a third of cases[24]. Spirometry was stable or improved over the

3 years of follow up. Whether this reflects better treatment, biological predisposition, a pattern of intermittent rather than progressive deterioration or simply the many different pathways by which each patient reaches that degree of airflow obstruction is not known. However it does offer a more optimistic vision of what is possible for COPD sufferers in the early part of the 21st century. The next generation of studies will need to understand these data better and should focus on increasing the number of people who can live with rather than die from chronic obstructive pulmonary disease.

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* = co-author not shown here; ** = senior author not shown here

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A

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

GOLD Executive Summary

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Chronic obstructive pulmonary disease (COPD) remains a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States, and is projected to rank fifth in 2020 in burden of disease worldwide, according to a study published by the World Bank/World Health Organization. Yet, COPD remains relatively unknown or ignored by the public as well as public health and government officials. In 1998, in an effort to bring more attention to COPD, its management, and its prevention, a committed group of scientists encouraged the U.S. National Heart, Lung, and Blood Institute and the World Health Organization to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Among the important objectives of GOLD are to increase awareness of COPD and to help the millions of people who suffer from this disease and die prematurely of it or its complications. The first step in the GOLD program was to prepare a consensus report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, published in 2001. The present, newly revised document follows the same format as the original consensus report, but has been updated to reflect the many publications on COPD that have appeared. GOLD national leaders, a network of international experts, have initiated investigations of the causes and prevalence of COPD in their countries, and developed innovative approaches for the dissemination and implementation of COPD management guidelines. We appreciate the enormous amount of work the GOLD national leaders have done on behalf of their patients with COPD. Despite the achievements in the 5 years since the GOLD report was originally published, considerable additional work is ahead of us if we are to control this major public health problem. The GOLD initiative will continue to bring COPD to the attention of governments, public health officials, health care workers, and the general public, but a concerted effort by all involved in health care will be necessary.

Keywords: COPD; guidelines; human; chronic disease

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely of it or its complications. The goals of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) are to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy, and to encourage an expanded level of research interest in this highly prevalent disease.

One strategy to help achieve the objectives of GOLD is to provide health care workers, health care authorities, and the general public with state-of-the-art information about COPD and specific recommendations on the most appropriate management and prevention strategies. The GOLD report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, is based on the best-validated current concepts of COPD pathogenesis and the available evidence on the most appropriate management and prevention strategies. A major part of the GOLD report is devoted to the clinical management of COPD and presents a management plan with four components: (*1*) assess and monitor disease, (*2*) reduce risk factors, (*3*) manage stable COPD, and (*4*) manage exacerbations. A new section at the end of the document will assist readers in translating guideline recommendations to the context of (primary) care.

GOLD is a partner organization in a program launched in March 2006 by the World Health Organization's Global Alliance Against Chronic Respiratory Diseases (GARD). Through the work of the GOLD committees, and in cooperation with GARD initiatives, progress toward better care for all patients with COPD should be substantial in the next decade.

Methodology and Summary of New Recommendations

After the release of the 2001 GOLD report, a science committee was formed and charged with keeping the GOLD documents up-to-date by reviewing published research, evaluating the impact of this research on the management recommendations in the GOLD documents, and posting yearly updates of these documents on the GOLD website (www.goldcopd.org). The methodology is described in each update (*see, e.g.*, the 2005 update in Reference 3 and the APPENDIX in the online supplement).

In January 2005, the GOLD science committee initiated preparation of this revised 2006 document on the basis of the most current scientific literature. Multiple meetings were held, including several with GOLD national leaders to discuss concepts and new recommendations. Before its publications, several reviewers were invited to submit comments.

A summary of the issues presented in this report include the following:

1. Recognition that COPD is characterized by chronic airflow limitation and a range of pathologic changes in the lung, some significant extrapulmonary effects, and important comorbidities that may contribute to the severity of the disease in individual patients.
2. In the definition of COPD, the phrase "preventable and treatable" has been incorporated following the American Thoracic Society/European Respiratory Society recommendations to recognize the need to present a positive outlook for patients, to encourage the health care community to take a more active role in developing programs for COPD prevention, and to stimulate effective management programs to treat those with the disease.
3. The spirometric classification of severity of COPD now includes four stages: stage I, mild; stage II, moderate; stage III, severe; stage IV, very severe. A fifth category, "stage 0, at risk," that appeared in the 2001 report is no longer included as a stage of COPD, as there is incomplete evidence that the individuals who meet the definition of "at risk" (chronic cough and sputum production, normal spirometry) necessarily progress on to stage I. Nevertheless, the importance of the public health message that chronic cough and sputum are not normal is unchanged.
4. The spirometric classification of severity continues to recommend use of the fixed ratio post-bronchodilator $FEV_1/FVC < 0.7$ to define airflow limitation. Using the fixed ratio (FEV_1/FVC) is particularly problematic in patients with milder disease who are elderly because the normal process of aging affects lung volumes. Post-bronchodilator reference values in this population are urgently needed to avoid potential overdiagnosis.
5. Section 2, BURDEN OF COPD, provides references to published data from prevalence surveys to estimate that about 15 to 25% of adults aged 40 years and older may have airflow limitation classified as stage I mild COPD or higher and that the prevalence of COPD (stage I, mild COPD and higher) is appreciably higher in smokers and ex-smokers than in nonsmokers, in those over 40 years compared with those younger than 40, and higher in men than in women. The section also provides new data on COPD morbidity and mortality.
6. Cigarette smoke is the most commonly encountered risk factor for COPD and elimination of this risk factor is an important step toward prevention and control of COPD. However, other risk factors for COPD should be taken into account where possible, including occupational dusts and chemicals, and indoor air pollution from biomass cooking and heating in poorly ventilated dwellings—the latter especially among women in developing countries.
7. The section on pathology, pathogenesis, and pathophysiology, continues with the theme that inhaled cigarette smoke and other noxious particles cause lung inflammation, a normal response which appears to be amplified in patients who develop COPD. The section has been considerably updated and revised.
8. Management of COPD continues to be presented in four components: (*1*) assess and monitor disease, (*2*) reduce risk factors, (*3*) manage stable COPD, and (*4*) manage exacerbations. All components have been updated on the basis of recently published literature. Throughout it is emphasized that the overall approach to managing stable COPD should be individualized to address symptoms and improve quality of life.
9. In COMPONENT 4, MANAGE EXACERBATIONS, a COPD exacerbation is defined as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD."

10. It is widely recognized that a wide spectrum of health care providers is required to ensure that COPD is diagnosed accurately, and that individuals who have COPD are treated effectively. The identification of effective health care teams will depend on the local health care system, and much work remains to identify how best to build these health care teams. A section on COPD implementation programs and issues for clinical practice has been included but it remains a field that requires considerable attention.

Levels of Evidence

Levels of evidence are assigned to management recommendations where appropriate in subsections of section 3 that discuss COPD management, with the system used in previous GOLD reports (Table 1). Evidence levels are enclosed in parentheses after the relevant statement—for example, (Evidence A).

1. DEFINITION, CLASSIFICATION OF SEVERITY, AND MECHANISMS OF COPD

Definition

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Airflow limitation is best measured by spirometry, because this is the most widely available, reproducible test of lung function.

Because COPD often develops in longtime smokers in middle age, patients often have a variety of other diseases related to either smoking or aging (4). COPD itself also has significant extrapulmonary (systemic) effects that lead to comorbid conditions (5). Thus, COPD should be managed with careful attention also paid to comorbidities and their effect on the patient's quality of life. A careful differential diagnosis and comprehensive assessment of severity of comorbid conditions should be performed in every patient with chronic airflow limitation.

Spirometric Classification of Severity and Stages of COPD

For educational reasons, a simple spirometric classification of disease severity into four stages is recommended (Table 2). Spirometry is essential for diagnosis and provides a useful description of the severity of pathologic changes in COPD. Specific spirometric cut points (e.g., post-bronchodilator FEV_1/FVC ratio < 0.70 or $FEV_1 < 80$, 50, or 30% predicted) are used for purposes of simplicity; these cut points have not been clinically validated. A study in a random population sample found that the post-bronchodilator FEV_1/FVC exceeded 0.70 in all age groups, supporting the use of this fixed ratio (6). However, because the process of aging does affect lung volumes, the use of this fixed ratio may result in overdiagnosis of COPD in the elderly, especially in those with mild disease.

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production. Chronic cough and sputum production may precede the development of airflow limitation by many years. This pattern offers a unique opportunity to identify smokers and others at risk for COPD, and to intervene when the disease is not yet a major health problem. Conversely, significant airflow limitation may develop without chronic cough and sputum production.

Stage I: mild COPD: Characterized by mild airflow limitation ($FEV_1/FVC < 0.70$, $FEV_1 \geq 80\%$ predicted). Symptoms of chronic cough and sputum production may be present, but not always. At this stage, the individual is usually unaware that his or her lung function is abnormal.

Stage II: moderate COPD: Characterized by worsening airflow limitation ($FEV_1/FVC < 0.70$, $50\% \leq FEV_1 < 80\%$ predicted), with shortness of breath typically developing on exertion and cough and sputum production sometimes also present. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease.

Stage III: severe COPD: Characterized by further worsening of airflow limitation ($FEV_1/FVC < 0.70$, $30\% \leq FEV_1 < 50\%$ predicted), greater shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations that almost always have an impact on patients' quality of life.

TABLE 1. DESCRIPTION OF LEVELS OF EVIDENCE

Evidence Category	Sources of Evidence	Definition
A	RCTs. Rich body of data.	Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	RCTs. Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, *post hoc* or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials. Observational studies.	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgment.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The panel consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

Definition of abbreviation: RCT = randomized controlled trial.

TABLE 2. SPIROMETRIC CLASSIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE SEVERITY BASED ON POST-BRONCHODILATOR FEV_1

Stage I: mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
Stage II: moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
Stage III: severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
Stage IV: very severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted *or* $FEV_1 < 50\%$ predicted plus chronic respiratory failure*

* Respiratory failure: arterial partial pressure of oxygen (Pa_{O_2}) < 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 (Pa_{CO_2}) > 6.7 kPa (50 mm Hg) while breathing air at sea level.

Stage IV: very severe COPD: Characterized by severe airflow limitation ($FEV_1/FVC < 0.70$, $FEV_1 < 30\%$ predicted *or* $FEV_1 < 50\%$ predicted plus the presence of chronic respiratory failure). Respiratory failure is defined as an arterial partial pressure of O_2 (Pa_{O_2}) less than 8.0 kPa (60 mm Hg), with or without an arterial partial pressure of CO_2 (Pa_{CO_2}) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. Respiratory failure may also lead to effects on the heart such as cor pulmonale (right heart failure). Clinical signs of cor pulmonale include elevation of the jugular venous pressure and pitting ankle edema. Patients may have stage IV COPD even if their FEV_1 is greater than 30% predicted, whenever these complications are present. At this stage, quality of life is very appreciably impaired and exacerbations may be life threatening.

Although asthma can usually be distinguished from COPD, in some individuals with chronic respiratory symptoms and fixed airflow limitation it remains difficult to differentiate the two diseases. In many developing countries, both pulmonary tuberculosis and COPD are common (7). In countries where tuberculosis is very common, respiratory abnormalities may be too readily attributed to this disease (8). Conversely, where the rate of tuberculosis is greatly diminished, the possible diagnosis of this disease is sometimes overlooked. Therefore, in all subjects with symptoms of COPD, a possible diagnosis of tuberculosis should be considered, especially in areas where this disease is known to be prevalent (9).

Pathology, Pathogenesis, and Pathophysiology

Pathologic changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature (10). The pathologic changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation.

The inflammation in the respiratory tract of patients with COPD appears to be an amplification of the normal inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. The mechanisms for this amplification are not yet understood but may be genetically determined. Some patients develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown (11). Lung inflammation is further amplified by oxidative stress and an excess of proteinases in the lung. Together, these mechanisms lead to the characteristic pathologic changes in COPD.

There is now a good understanding of how the underlying disease process in COPD leads to the characteristic physiologic abnormalities and symptoms. For example, decreased FEV_1 primarily results from inflammation and narrowing of peripheral airways and a dynamic airway collapse in more severe emphysema, whereas decreased gas transfer arises from the parenchymal destruction of emphysema. The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/FVC ratio, and probably with the accelerated decline in FEV_1 characteristic of COPD (4). Gas exchange abnormalities result in hypoxemia and hypercapnia, and have several mechanisms in COPD. In general, gas transfer worsens as the disease progresses. Mild to moderate pulmonary hypertension may develop late in the course of COPD and is due to hypoxic vasoconstriction of small pulmonary arteries. It is increasingly recognized that COPD involves several systemic features, particularly in patients with severe disease, and that these have a major impact on survival and comorbid diseases (12, 13).

2. BURDEN OF COPD

COPD prevalence, morbidity, and mortality vary across countries and across different groups within countries but, in general, are directly related to the prevalence of tobacco smoking, although, in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population.

Epidemiology

In the past, imprecise and variable definitions of COPD have made it difficult to quantify prevalence, morbidity, and mortality. Furthermore, the underrecognition and underdiagnosis of COPD lead to significant underreporting. The extent of the underreporting varies across countries and depends on the level of awareness and understanding of COPD among health professionals, the organization of health care services to cope with chronic diseases, and the availability of medications for the treatment of COPD (14).

Prevalence. Many sources of variation can affect estimates of COPD prevalence, including sampling methods, response rates, quality control of spirometry, and whether spirometry is performed pre- or post-bronchodilator. Despite these complexities, data are emerging that enable some conclusions to be drawn regarding COPD prevalence. A prevalence study in Latin America (19), a systematic review and meta-analysis of studies performed in 28 countries between 1990 and 2004 (15), and an additional study from Japan (16) provide evidence that the prevalence of COPD (stage I, mild COPD and higher) is appreciably higher in smokers and ex-smokers compared with nonsmokers, in those older than 40 years compared with those younger than 40 years, and in men compared with women.

Morbidity. Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. Although COPD databases for these outcome parameters are less readily available and usually less reliable than mortality databases, the limited data available indicate that morbidity due to COPD increases with age and is greater in men than in women (17, 18). COPD in its early stages (stages I and II) is usually not recognized, diagnosed, or treated, and therefore may not be included as a diagnosis in a patient's medical record.

Morbidity from COPD may be affected by other comorbid chronic conditions (20) (e.g., musculoskeletal disease, diabetes

mellitus) that are not directly related to COPD but nevertheless may have an impact on the patient's health status, or may interfere with COPD management. In patients with more advanced disease (stages III and IV), morbidity from COPD may be misattributed to another comorbid condition.

Mortality. COPD is one of the most important causes of death in most countries. The Global Burden of Disease Study (2, 21, 22) has projected that COPD, which ranked sixth as the cause of death in 1990, will become the third leading cause of death worldwide by 2020. This increased mortality is driven by the expanding epidemic of smoking and the changing demographics in most countries, with more of the population living longer.

Economic and Social Burden of COPD

COPD is a costly disease. In developed countries, exacerbations of COPD account for the greatest burden on the health care system. In the European Union, the total *direct* costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56% (€38.6 billion) of this cost of respiratory disease (23). In the United States in 2002, the direct costs of COPD were $18 billion and the indirect costs totaled $14.1 billion (1). Costs per patient will vary across countries because these costs depend on how health care is provided and paid (24). Not surprisingly, there is a striking direct relationship between the severity of COPD and the cost of care (25), and the distribution of costs changes as the disease progresses.

Risk Factors

Identification of cigarette smoking as the most commonly encountered risk factor for COPD has led to the incorporation of smoking cessation programs as a key element of COPD prevention, as well as an important intervention for patients who already have the disease. However, although smoking is the best-studied COPD risk factor, it is not the only one and there is consistent evidence from epidemiologic studies that nonsmokers may develop chronic airflow obstruction (26, 27) (Figure 1).

Genes. As the understanding of the importance of risk factors for COPD has grown, so has the recognition that essentially all risk for COPD results from a gene–environment interaction. The genetic risk factor that is best documented is a severe hereditary deficiency of α_1-antitrypsin (28), a major circulating inhibitor of serine proteases. This rare recessive trait is most commonly seen in individuals of northern European origin (29).

Genetic association studies have implicated a variety of genes in COPD pathogenesis. However, the results of these genetic association studies have been largely inconsistent, and functional genetic variants influencing the development of COPD (other than α_1-antitrypsin deficiency) have not been definitively identified (30).

Inhalational exposures. Tobacco smoke. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV_1, and a greater COPD mortality rate than nonsmokers. Pipe and cigar smokers have greater COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers (31). Other types of tobacco smoking popular in various countries are also risk factors for COPD (32, 33). Not all smokers develop clinically significant COPD, which suggests that genetic factors must modify each individual's risk (34). Passive exposure to cigarette smoke may also contribute to respiratory symptoms (35) and COPD (36) by increasing the lungs' total burden of inhaled particles and gases (37, 38). Smoking during pregnancy may also pose a risk for the fetus, by affecting lung growth and development *in utero* and possibly the priming of the immune system (39, 40).

Occupational dusts and chemicals. Occupational exposures include organic and inorganic dusts and chemical agents and fumes. A statement published by the American Thoracic Society concluded that occupational exposures account for 10 to 20% of either symptoms or functional impairment consistent with COPD (41).

Indoor and outdoor air pollution. The evidence that indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD (especially among women in developing countries) continues to grow (42–48), with case-control studies (47, 48) and other designed studies now available. High levels of urban air pollution are harmful to individuals with existing heart or lung disease, but the role of outdoor air pollution in causing COPD is unclear.

Sex. Studies from developed countries (1, 49) show that the prevalence of the disease is now almost equal in men and

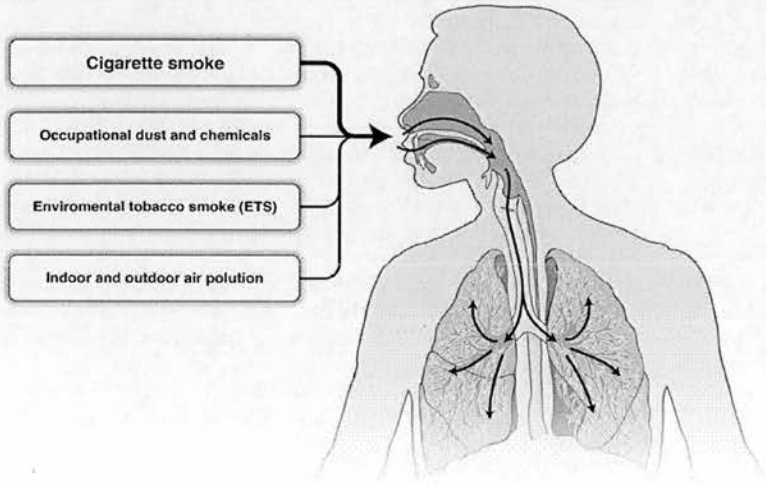

Figure 1. Chronic obstructive pulmonary disease risk is related to the total burden of inhaled particles.

women, probably reflecting the changing patterns of tobacco smoking. Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men (50–52).

Infection. A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood (53–55). However, susceptibility to viral infections may be related to another factor, such as low birth weight, that itself is related to COPD.

Socioeconomic status. There is evidence that the risk of developing COPD is inversely related to socioeconomic status (56). It is not clear, however, whether this pattern reflects exposures to cigarette smoke, indoor and outdoor air pollutants, crowding, poor nutrition, or other factors that are related to low socioeconomic status (57, 58).

3. THE FOUR COMPONENTS OF COPD MANAGEMENT

Introduction

An effective COPD management plan includes four components: (*1*) assess and monitor disease, (*2*) reduce risk factors, (*3*) manage stable COPD, and (*4*) manage exacerbations. Although disease prevention is the ultimate goal, once COPD has been diagnosed, effective management should be aimed at the following goals:

- Relieve symptoms
- Prevent disease progression
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

These goals should be reached with minimal side effects from treatment, a particular challenge in patients with COPD because they commonly have comorbidities. The extent to which these goals can be realized varies with each individual, and some treatments will produce benefits in more than one area. In selecting a treatment plan, the benefits and risks to the individual, and the costs, direct and indirect, to the individual, his or her family, and the community must be considered.

Patients should be identified as early in the course of the disease as possible, and certainly before the end stage of the illness when disability is substantial. Access to spirometry is key to the diagnosis of COPD and should be available to health care workers who care for patients with COPD. However, the benefits of community-based spirometric screening, of either the general population or smokers, are still unclear.

Educating patients, physicians, and the public to recognize that cough, sputum production, and especially breathlessness are not trivial symptoms is an essential aspect of the public health care of this disease.

Reduction of therapy once symptom control has been achieved is not normally possible in COPD. Further deterioration of lung function usually requires the progressive introduction of more treatments, both pharmacologic and nonpharmacologic, to attempt to limit the impact of these changes. Exacerbations of signs and symptoms, a hallmark of COPD, impair patients' quality of life and decrease their health status. Appropriate treatment and measures to prevent further exacerbations should be implemented as quickly as possible.

Component 1: Assess and Monitor Disease

KEY POINTS

- A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. The diagnosis should be confirmed by spirometry.
- For the diagnosis and assessment of COPD, spirometry is the gold standard because it is the most reproducible, standardized, and objective way of measuring airflow limitation. A post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of airflow limitation that is not fully reversible.
- Health care workers involved in the diagnosis and management of patients with COPD should have access to spirometry.
- Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality, and the presence of complications.
- Measurement of arterial blood gas tensions should be considered in all patients with $FEV_1 < 50\%$ predicted or clinical signs suggestive of respiratory failure or right heart failure.
- COPD is usually a progressive disease and lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify any complications that may develop.
- Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa.

Initial diagnosis. A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (Table 3). The diagnosis should be confirmed by spirometry.

ASSESSMENT OF SYMPTOMS. Dyspnea, the hallmark symptom of COPD, is the reason most patients seek medical attention and is a major cause of disability and anxiety associated with the disease. As lung function deteriorates, breathlessness becomes more intrusive. Chronic cough, often the first symptom of COPD to develop (59) and often predating the onset of dyspnea, may be intermittent, but later is present every day, often throughout the day. In some cases, significant airflow limitation may develop without the presence of a cough. Patients with COPD commonly raise small quantities of tenacious sputum after coughing bouts. Wheezing and chest tightness are nonspecific symptoms that may vary between days, and over the course of a single day. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD. Weight loss, anorexia, and psychiatric morbidity, especially symptoms of depression and/or anxiety, are common problems in advanced COPD (60, 61).

MEDICAL HISTORY. A detailed medical history of a new patient known or believed to have COPD should assess the following:

- Exposure to risk factors

TABLE 3. KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Consider COPD, and perform spirometry, if any of these indicators are present in an individual. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

Dyspnea that is	Progressive (worsens over time) Usually worse with exercise Persistent (present every day) Described by the patient as an "increased effort to breathe," "heaviness," "air hunger," or "gasping
Chronic cough	May be intermittent and may be unproductive
Chronic sputum production	Any pattern of chronic sputum production may indicate COPD
History of exposure to risk factors, especially,	Tobacco smoke Occupational dusts and chemicals Smoke from home cooking and heating fuels

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

- Past medical history, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other respiratory diseases
- Family history of COPD or other chronic respiratory disease
- Pattern of symptom development
- History of exacerbations or previous hospitalizations for respiratory disorder
- Presence of comorbidities, such as heart disease, malignancies, osteoporosis, and muscloskeletal disorders, which may also contribute to restriction of activity (62)
- Appropriateness of current medical treatments
- Impact of disease on patient's life, including limitation of activity, missed work and economic impact, effect on family routines, feelings of depression or anxiety
- Social and family support available to the patient
- Possibilities for reducing risk factors, especially smoking cessation

PHYSICAL EXAMINATION. Although an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred (63, 64), and their detection has a relatively low sensitivity and specificity.

MEASUREMENT OF AIRFLOW LIMITATION (SPIROMETRY). Spirometry should be undertaken in all patients who may have COPD. Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (FVC) and the volume of air exhaled during the first second of this maneuver (FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Spirometry measurements are evaluated by comparison with reference values (65) based on age, height, sex, and race (use appropriate reference values; e.g., *see* Reference 65). Patients with COPD typically show a decrease in both FEV_1 and FVC. The presence of airflow limitation is defined by a post-bronchodilator $FEV_1/FVC < 0.70$. This approach is pragmatic in view of the fact that universally applicable reference values for FEV_1 and FVC are not available. Where possible, values should be compared with age-related normal values to avoid overdiagnosis of COPD in the elderly (66). Using the fixed ratio (FEV_1/FVC) is particularly problematic in patients with milder COPD who are elderly because the normal process of aging affects lung volumes.

ASSESSMENT OF COPD SEVERITY. Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality (Table 2), and the presence of complications such as respiratory failure, right heart failure, weight loss, and arterial hypoxemia.

ADDITIONAL INVESTIGATIONS. For patients diagnosed with stage II, moderate, COPD and beyond, the following additional investigations may be considered.

Bronchodilator reversibility testing. Despite earlier hopes, neither bronchodilator nor oral glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV_1, deterioration of health status, or frequency of exacerbations (67, 68) in patients with a clinical diagnosis of COPD and abnormal spirometry (68). In some cases (e.g., a patient with an atypical history such as asthma in childhood and regular night waking with cough or wheeze), a clinician may wish to perform a bronchodilator and/or glucocorticosteroid reversibility test.

Chest X-ray. An abnormal chest X-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities, such as cardiac failure. Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, high-resolution CT scanning might help in the differential diagnosis. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary because the distribution of emphysema is one of the most important determinants of surgical suitability (69).

Arterial blood gas measurement. In advanced COPD, measurement of arterial blood gases while the patient is breathing air is important. This test should be performed in stable patients with $FEV_1 < 50\%$ predicted or with clinical signs suggestive of respiratory failure or right heart failure.

α_1-Antitrypsin deficiency screening. In patients of Caucasian descent who develop COPD at a young age (< 45 yr) or who have a strong family history of the disease, it may be valuable to identify coexisting α_1-antitrypsin deficiency. This could lead to family screening or appropriate counseling.

DIFFERENTIAL DIAGNOSIS. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiologic testing techniques, and it is assumed that asthma and COPD coexist in these patients. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD (Table 4).

Ongoing monitoring and assessment. MONITOR DISEASE PROGRESSION AND DEVELOPMENT OF COMPLICATIONS. COPD is usually a progressive disease. Lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify any complications that may develop.

Follow-up visits should include a physical examination and discussion of symptoms, particularly any new or worsening symptoms. Spirometry should be performed if there is a substantial increase in symptoms or a complication. The development of respiratory failure is indicated by a $Pa_{O_2} < 8.0$ kPa (60 mm Hg) with or without $Pa_{CO_2} > 6.7$ kPa (50 mm Hg) in arterial blood gas measurements made while breathing air at sea level. Measurement of pulmonary arterial pressure is not recommended in clinical practice as it does not add practical information beyond that obtained from a knowledge of Pa_{O_2}.

MONITOR PHARMACOTHERAPY AND OTHER MEDICAL TREATMENT. To adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored.

MONITOR EXACERBATION HISTORY. Frequency, severity, and likely causes of exacerbations should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation.

MONITOR COMORBIDITIES. Comorbidities are common in COPD and may become harder to manage when COPD is present, either because COPD adds to the total level of disability or because COPD therapy adversely affects the comorbid disorder. Until more integrated guidance about disease management for specific comorbid problems becomes available, the focus should be on identification and management of these individual problems.

TABLE 4. DIFFERENTIAL DIAGNOSIS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Diagnosis	Suggestive Features
COPD	Onset in midlife
	Symptoms slowly progressive
	Long history of tobacco smoking
	Dyspnea during exercise
	Largely irreversible airflow limitation
Asthma	Onset early in life (often childhood)
	Symptoms vary from day to day
	Symptoms at night/early morning
	Allergy, rhinitis, and/or eczema also present
	Family history of asthma
	Largely reversible airflow limitation
Congestive heart failure	Nonspecific basilar crackles on auscultation
	Chest X-ray shows dilated heart, pulmonary edema
	Pulmonary function tests indicate volume restriction, not airflow limitation
Bronchiectasis	Large volumes of purulent sputum
	Commonly associated with bacterial infection
	Coarse crackles/clubbing on auscultation
	Chest X-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages
	Chest X-ray shows lung infiltrate
	Microbiological confirmation
	High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset in younger age, nonsmokers
	May have history of rheumatoid arthritis or fume exposure
	CT on expiration shows hypodense areas
Diffuse panbronchiolitis	Most patients are male and nonsmokers
	Almost all have chronic sinusitis
	Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; HRCT = high-resolution computed tomography.

These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.

Component 2: Reduce Risk Factors

KEY POINTS

- Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD.
- Smoking cessation is the single most effective—and cost-effective—intervention in most people to reduce the risk of developing COPD and stop its progression (**Evidence A**).
- Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel.
- Efforts to reduce smoking through public health initiatives should also focus on passive smoking to minimize risks for nonsmokers.
- Many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases.
- Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients.

Smoking prevention and cessation. Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel, including health care providers, community activities, and schools, and radio, television, and print media. Legislation to establish smoke-free schools, public facilities, and work environments should be developed and implemented by government officials and public health workers, and encouraged by the public.

SMOKING CESSATION INTERVENTION PROCESS. Smoking cessation is the single most effective—and cost-effective—way to reduce exposure to COPD risk factors. All smokers—including those who may be at risk for COPD as well as those who already have the disease—should be offered the most intensive smoking cessation intervention feasible. Even a brief (3 min) period of counseling to urge a smoker to quit results in smoking cessation rates of 5 to 10% (70). At the very least, this should be done for every smoker at every health care provider visit (70, 71).

Guidelines for smoking cessation entitled "Treating Tobacco Use and Dependence: A Clinical Practice Guideline" were published by the U.S. Public Health Service (72) and recommend a five-step program for intervention (Table 5), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking (72–75).

PHARMACOTHERAPY. Numerous effective pharmacotherapies for smoking cessation now exist (72, 73, 76) (Evidence A), and pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Numerous studies indicate that nicotine replacement therapy in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates (72, 77).

The antidepressants bupropion (78) and nortriptyline have also been shown to increase long-term quit rates (76, 77, 79), but should always be used as one element in a supportive intervention program rather than on their own. The effectiveness of the antihypertensive drug clonidine is limited by side effects (77). Varenicline, a nicotinic acetylcholine receptor partial

agonist that aids smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine, has been demonstrated to be safe and efficacious (80–82). Special consideration should be given before using pharmacotherapy in the following selected populations: people with medical contraindications, light smokers (<10 cigarettes/d), and pregnant and adolescent smokers.

Occupational exposures. Although it is not known how many individuals are at risk of developing respiratory disease from occupational exposures in either developing or developed countries, many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases (83–85).

The main emphasis should be on primary prevention, which is best achieved by the elimination or reduction of exposures to various substances in the workplace. Secondary prevention, achieved through surveillance and early case detection, is also of great importance.

Indoor and outdoor air pollution. Individuals experience diverse indoor and outdoor environments throughout the day, each of which has its own unique set of air contaminants and particulates that cause adverse effects on lung function (86). Although outdoor and indoor air pollution are generally considered separately, the concept of total personal exposure may be more relevant for COPD. Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients. At the national level, achieving a set level of air quality standards should be a high priority; this goal will normally require legislative action. Reduction of exposure to smoke from biomass fuel, particularly among women and children, is a crucial goal to reduce the prevalence of COPD worldwide. Although efficient nonpolluting cooking stoves have been developed, their adoption has been slow due to social customs and cost.

The health care provider should consider COPD risk factors, including smoking history, family history, exposure to indoor/outdoor pollution, and socioeconomic status, for each individual patient. Those who are at high risk should avoid vigorous exercise outdoors during pollution episodes. Persons with advanced COPD should monitor public announcements of air quality and be aware that staying indoors when air quality is poor may help reduce their symptoms. If various solid fuels are used for cooking and heating, adequate ventilation should be encouraged. Under most circumstances, vigorous attempts should be made to reduce exposure through reducing workplace emissions and improving ventilation measures, rather than simply using respiratory protection to reduce the risks of ambient air pollution. Air cleaners have not been shown to have health benefits, whether directed at pollutants generated by indoor sources or at those brought in with outdoor air.

TABLE 5. BRIEF STRATEGIES TO HELP THE PATIENT WHO IS WILLING TO QUIT

1. ASK: Systematically identify all tobacco users at every visit.
   Implement an officewide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco use status is queried and documented.
2. ADVISE: Strongly urge all tobacco users to quit.
   In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. ASSESS: Determine willingness to make a quit attempt.
   Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 d).
4. ASSIST: Aid the patient in quitting.
   Help the patient with a quit plan; provide practical counseling; provide intratreatment social support; help the patient obtain extratreatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
5. ARRANGE: Schedule follow-up contact.
   Schedule follow-up contact, either in person or via telephone.

Data from References 72–75.

Component 3: Manage Stable COPD

KEY POINTS

- The overall approach to managing stable COPD should be individualized to address symptoms and improve quality of life.
- For patients with COPD, health education plays an important role in smoking cessation (Evidence A) and can also play a role in improving skills, ability to cope with illness, and health status.
- None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease (Evidence A). Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications.
- Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations.
- The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used singly or in combination (Evidence A).
- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (Evidence A).
- The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic patients with COPD with an $FEV_1 < 50\%$ predicted (stage III, severe COPD, and stage IV, very severe COPD) and repeated exacerbations (Evidence A).
- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (Evidence A).
- In patients with COPD, influenza vaccines can reduce serious illness (Evidence A). Pneumococcal polysaccharide vaccine is recommended for patients with COPD who are 65 years and older and for patients with COPD who are younger than age 65 with an $FEV_1 < 40\%$ predicted (Evidence B).
- All patients with COPD benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (Evidence A).
- The long-term administration of oxygen (> 15 h/d) to patients with chronic respiratory failure has been shown to increase survival (Evidence A).

Introduction. The overall approach to managing stable COPD should be characterized by an increase in treatment, depending on the severity of the disease and the clinical status of the patient. Management of COPD is based on an individualized assessment of disease severity and response to various therapies. The classification of severity of stable COPD incorporates an individualized assessment of disease severity and therapeutic response into the management strategy. The severity of airflow limitation provides a general guide to the use of some treatments, but the

selection of therapy is predominantly determined by the patient's symptoms and clinical presentation. Treatment also depends on the patient's educational level and willingness to apply the recommended management, on cultural and local practice conditions, and on the availability of medications.

Education. Although patient education is generally regarded as an essential component of care for any chronic disease, assessment of the value of education in COPD may be difficult because of the relatively long time required to achieve improvements in objective measurements of lung function. Patient education alone does not improve exercise performance or lung function (87–90) (Evidence B), but it can play a role in improving skills, ability to cope with illness, and health status (91). Patient education regarding smoking cessation has the greatest capacity to influence the natural history of COPD (Evidence A). Education also improves patient response to exacerbations (92, 93) (Evidence B). Prospective end-of-life discussions can lead to understanding of advance directives and effective therapeutic decisions at the end of life (94) (Evidence B).

Ideally, educational messages should be incorporated into all aspects of care for COPD and may take place in many settings: consultations with physicians or other health care workers, home-care or outreach programs, and comprehensive pulmonary rehabilitation programs. Education should be tailored to the needs and environment of the individual patient, interactive, directed at improving quality of life, simple to follow, practical, and appropriate to the intellectual and social skills of the patient and the caregivers. The topics that seem most appropriate for an education program include the following: smoking cessation; basic information about COPD and pathophysiology of the disease, general approach to therapy and specific aspects of medical treatment, self-management skills, strategies to help minimize dyspnea, advice about when to seek help, self-management and decision making during exacerbations, and advance directives and end-of-life issues.

Pharmacologic treatments. Pharmacologic therapy is used to prevent and control symptoms (Figure 2), reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications (Table 6) for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease (51, 95–97) (Evidence A). However, this should not preclude efforts to use medications to control symptoms.

Bronchodilators. Bronchodilator medications are central to the symptomatic management of COPD (98–101) (Evidence A) (Table 7). They are given either on an as-needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. The side effects of bronchodilator therapy are pharmacologically predictable and dose dependent. Adverse effects are less likely, and resolve more rapidly after treatment withdrawal, with inhaled than with oral treatment. When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique are essential.

Bronchodilator drugs commonly used in treating COPD include β_2-agonists, anticholinergics, and methylxanthines. The choice depends on the availability of the medications and the patient's response. All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV_1 (102–105) (Evidence A).

Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (106–109) (Evidence A). Regular use of a long-acting β_2-agonist (107) or a short- or long-acting anticholinergic improves health status (106–108). Treatment with a long-acting inhaled anticholinergic drug reduces the rate of COPD exacerbations (110) and improves the effectiveness of pulmonary rehabilitation (111). Theophylline is effective in COPD, but, due to its potential toxicity, inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. A combination of a short-acting β_2-agonist and an anticholinergic produces greater and more sustained improvements in FEV_1 than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment (112–114) (Evidence A).

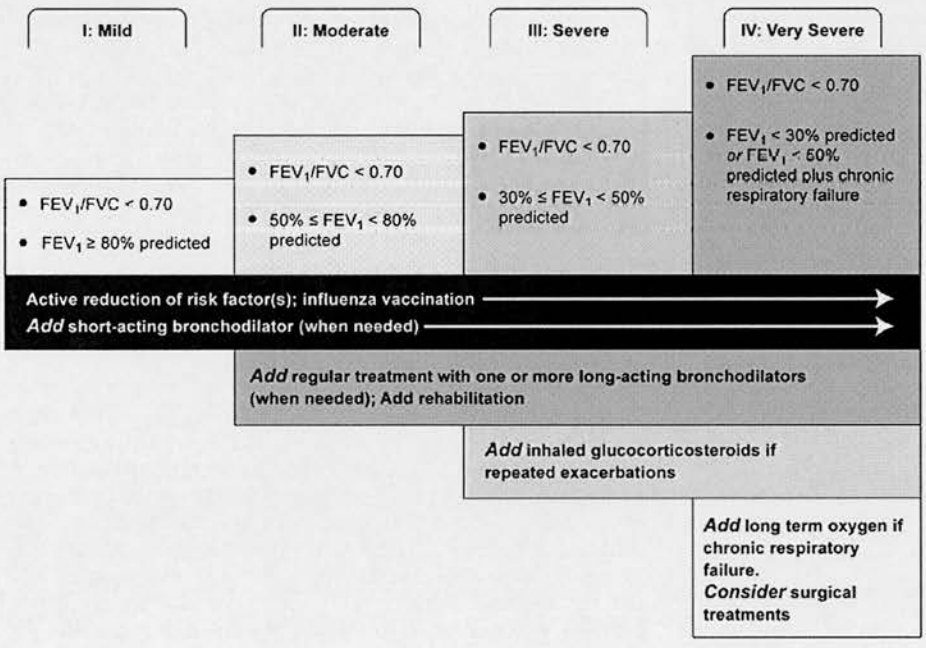

Figure 2. Therapy at each stage of chronic obstructive pulmonary disease (COPD). Post-bronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD.

TABLE 6. COMMONLY USED FORMULATIONS OF MEDICATIONS USED IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Medication	Inhaler (μg)	Solution for Nebulizer (mg/ml)	Oral	Vials for Injection (mg)	Duration of Action (h)
β_2-Agonists					
Short-acting					
Fenoterol	100–200 (MDI)	1	0.5% (syrup)		4–6
Salbutamol (albuterol)	100, 200 (MDI and DPI)	5	5 mg (pill) 0.24% (syrup)	0.1, 0.5	4–6
Terbutaline	400, 500 (DPI)			0.2, 0.25	4–6
Long-acting					
Formoterol	4.5–12 (MDI and DPI)				12+
Salmeterol	25–50 (MDI and DPI)				12+
Anticholinergics					
Short-acting					
Ipatropium bromide	20, 40 (MDI)	0.25-0.5			6–8
Oxitropium bromide	100 (MDI)	1.5			7–9
Long-acting					
Tiotropium	18 (DPI)				24+
Combination short-acting β_2-agonists plus anticholinergic in one inhaler					
Fenoterol/ipratropium	200/80 (MDI)	1.25/0.5			6–8
Salbutamol/ipratropium	75/15 (MDI)	0.75/4.5			6–8
Methylxanthines					
Aminophylline			200–600 mg (pill)	240	Variable, up to 24
Theophylline (SR)			100–600 mg (pill)		Variable, up to 24
Inhaled glucocorticosteroids					
Beclomethasone	50–400 (MDI and DPI)	0.2-0.4			
Budesonide	100, 200, 400 (DPI)	0.20, 0.25, 0.5			
Fluticasone	50–500 (MDI and DPI)				
Triamcinolone	100 (MDI)	40		40	
Combination long-acting β_2-agonists plus glucocorticosteroids in one inhaler					
Formoterol/budesonide	4.5/160, 9/320 (DPI)				
Salmeterol/fluticasone	50/100, 250, 500 (DPI) 25/50, 125, 250 (MDI)				
Systemic glucocorticosteroids					
Prednisone			5–60 mg (pill)		
Methylprednisolone			4, 8, 16 mg (pill)		

Definition of abbreviation: DPI = dry powder inhaler; MDI = metered-dose inhaler; SR = slow release.

The combination of a β_2-agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function (112–118) and health status (112, 119). Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects are not a limiting factor. Detailed assessments of this approach have not been performed.

Dose–response relationships using the FEV_1 as the outcome are relatively flat with all classes of bronchodilators (98–101). Toxicity is also dose related. Increasing the dose of either a β_2-agonist or an anticholinergic by an order of magnitude, especially when given by a wet nebulizer, appears to provide subjective benefit in acute episodes (120) (Evidence B) but is not necessarily helpful in stable disease (121) (Evidence C).

When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique are essential. The choice of inhaler device will depend on availability, cost, the prescribing physician, and the skills and ability of the patient. Patients with COPD may have more problems in effective coordination and find it harder to use a simple metered-dose inhaler than do healthy volunteers or younger patients with asthma. It is essential to ensure that inhaler technique is correct and to recheck this at each visit.

GLUCOCORTICOSTEROIDS. Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV_1 in patients with COPD (95–97, 122). However, regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic patients with COPD with an $FEV_1 < 50\%$ predicted (stages III and IV) and repeated exacerbations (e.g., three in the last 3 yr) (123–126) (Evidence A). This treatment has been shown to reduce the frequency of exacerbations and thus improve health status (127) (Evidence A), and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients (128). Reanalysis of pooled data from several longer studies of inhaled glucocorticosteroids in COPD suggests that this treatment reduces all-cause mortality (129), but this conclusion requires confirmation in prospective studies before leading to a change in current treatment

TABLE 7. BRONCHODILATORS IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- Bronchodilator medications are central to symptom management in COPD.
- Inhaled therapy is preferred.
- The choice among β_2-agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects.
- Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
- Long-acting inhaled bronchodilators are more effective and convenient.
- Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

recommendations. An inhaled glucocorticosteroid combined with a long-acting β_2-agonist is more effective than the individual components (123, 125, 126, 130, 131) (Evidence A). The dose–response relationships and long-term safety of inhaled glucocorticosteroids in COPD are not known.

Long-term treatment with oral glucocorticosteroids is not recommended in COPD (Evidence A). A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy (132–134), which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD.

OTHER PHARMACOLOGIC TREATMENTS. *Vaccines.* Influenza vaccines can reduce serious illness (135) and death in patients with COPD by approximately 50% (136, 137) (Evidence A). Vaccines containing killed or live, inactivated viruses are recommended (138) because they are more effective in elderly patients with COPD (139). The strains are adjusted each year for appropriate effectiveness and should be given once each year (140). Pneumococcal polysaccharide vaccine is recommended for patients with COPD who are 65 years and older (141, 142). In addition, this vaccine has been shown to reduce the incidence of community-acquired pneumonia in patients with COPD who are younger than 65 years with an $FEV_1 < 40\%$ predicted (143) (Evidence B).

α_1-Antitrypsin augmentation therapy. Young patients with severe hereditary α_1-antitrypsin deficiency and established emphysema may be candidates for α_1-antitrypsin augmentation therapy. However, this therapy is very expensive, not available in most countries, and not recommended for patients with COPD that is unrelated to α_1-antitrypsin deficiency (Evidence C).

Antibiotics. Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD (144–146), and a study that examined the efficacy of chemoprophylaxis undertaken in the winter months over a period of 5 years concluded that there was no benefit (147). There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful (148, 149) (Evidence A).

Mucolytic (mucokinetic, mucoregulator) agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol). The regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results (150–152). Although a few patients with viscous sputum may benefit from mucolytics (153, 154), the overall benefits seem to be very small, and the widespread use of these agents cannot be recommended at present (Evidence D).

Antioxidant agents. Antioxidants, in particular N-acetylcysteine, have been reported in small studies to reduce the frequency of exacerbations, leading to speculation that these medications could have a role in the treatment of patients with recurrent exacerbations (155–158) (Evidence B). However, a large randomized controlled trial found no effect of N-acetylcysteine on the frequency of exacerbations, except in patients not treated with inhaled glucocorticosteroids (159).

Immunoregulators (immunostimulators, immunomodulators). Studies using an immunoregulator in COPD show a decrease in the severity and frequency of exacerbations (160, 161). However, additional studies to examine the long-term effects of this therapy are required before its regular use can be recommended (162).

Antitussives. Cough, although sometimes a troublesome symptom in COPD, has a significant protective role (163). Thus, the regular use of antitussives is not recommended in stable COPD (Evidence D).

Vasodilators. In patients with COPD, inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation–perfusion balance (164, 165). Therefore, based on the available evidence, nitric oxide is not indicated in stable COPD.

Narcotics (morphine). Oral and parenteral opioids are effective for treating dyspnea in patients with advanced COPD disease. There are insufficient data to conclude whether nebulized opioids are effective (166). However, some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects (167–171).

Others. Nedocromil, leukotriene modifiers, and alternative healing methods (e.g., herbal medicine, acupunture, homeopathy) have not been adequately tested in patients with COPD and thus cannot be recommended at this time.

Nonpharmacologic treatments. REHABILITATION. The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. To accomplish these goals, pulmonary rehabilitation covers a range of nonpulmonary problems that may not be adequately addressed by medical therapy for COPD. Such problems, which especially affect patients with stages II through IV COPD, include exercise deconditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss.

Although more information is needed on criteria for patient selection for pulmonary rehabilitation programs, patients with COPD at all stages of disease appear to benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (172) (Evidence A). Data suggest that these benefits can be sustained even after a single pulmonary rehabilitation program (173–175). Benefit does wane after a rehabilitation program ends, but if exercise training is maintained at home, the patient's health status remains above pre-rehabilitation levels (Evidence B). To date, there is no consensus on whether repeated rehabilitation courses enable patients to sustain the benefits gained through the initial course. Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings (176–178).

Ideally, pulmonary rehabilitation should involve several types of health professionals. The components of pulmonary rehabilitation vary widely from program to program, but a comprehensive pulmonary rehabilitation program includes exercise training, nutrition counseling, and education. Baseline and outcome assessments of each participant in a pulmonary rehabilitation program should be made to quantify individual gains and target areas for improvement. Assessments should include the following:

- Detailed history and physical examination
- Measurement of spirometry before and after use of a bronchodilator drug
- Assessment of exercise capacity
- Measurement of health status and impact of breathlessness
- Assessment of inspiratory and expiratory muscle strength and lower limb strength (e.g., quadriceps) in patients who suffer from muscle wasting

The first two assessments are important for establishing entry suitability and baseline status but are not used in outcome assessment. The last three assessments are baseline and outcome measures.

OXYGEN THERAPY The long-term administration of oxygen (> 15 h/d) to patients with chronic respiratory failure has been shown to increase survival (179, 180). It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state (181).

Long-term oxygen therapy is generally introduced in patients with stage IV COPD, who have

- Pa_{O_2} at or below 7.3 kPa (55 mm Hg) or Sa_{O_2} at or below 88%, with or without hypercapnia (Evidence B), *or*
- Pa_{O_2} between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or Sa_{O_2} of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%) (Evidence D).

The primary goal of oxygen therapy is to increase the baseline Pa_{O_2} to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce an Sa_{O_2} of at least 90%, which will preserve vital organ function by ensuring adequate delivery of oxygen. A decision about the use of long-term oxygen should be based on the waking Pa_{O_2} values. The prescription should always include the source of supplemental oxygen (gas or liquid), method of delivery, duration of use, and flow rate at rest, during exercise, and during sleep.

VENTILATORY SUPPORT. Although long-term noninvasive positive-pressure ventilation (NIPPV) cannot be recommended for the routine treatment of patients with chronic respiratory failure due to COPD, the combination of NIPPV with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in those with pronounced daytime hypercapnia (182).

SURGICAL TREATMENTS. *Bullectomy.* In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function (183) (Evidence C). A thoracic CT scan, arterial blood gas measurement, and comprehensive respiratory function tests are essential before making a decision regarding suitability for resection of a bulla.

Lung volume reduction surgery. A large multicenter study of 1,200 patients comparing lung volume reduction surgery with medical treatment has shown that after 4.3 years, patients with upper lobe emphysema and low exercise capacity who received the surgery had a greater survival rate than similar patients who received medical therapy (54 vs. 39.7%) (184). In addition, the surgery patients experienced greater improvements in their maximal work capacity and their health-related quality of life. The advantage of surgery over medical therapy was less significant among patients who had other emphysema distribution or high exercise capacity before treatment. Although the results of this study showed some very positive results of surgery in a select group of patients (69, 184), lung volume reduction surgery is an expensive palliative surgical procedure and can be recommended only in carefully selected patients.

Lung transplantation. In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity (185–188) (Evidence C). Criteria for referral for lung transplantation include FEV_1 < 35% predicted, Pa_{O_2} < 7.3–8.0 kPa (55–60 mm Hg), Pa_{CO_2} > 6.7 kPa (50 mm Hg), and secondary pulmonary hypertension (189, 190).

Special considerations. SURGERY IN COPD. Postoperative pulmonary complications are as important and common as postoperative cardiac complications and, consequently, are a key component of the increased risk posed by surgery in patients with COPD. The principal potential factors contributing to the risk include smoking, poor general health status, age, obesity, and COPD severity. A comprehensive definition of postoperative pulmonary complications should include only major pulmonary respiratory complications, namely lung infections, atelectasis, and/or increased airflow obstruction, all potentially resulting in acute respiratory failure and aggravation of underlying COPD (191–196).

Component 4: Manage Exacerbations

KEY POINTS

- An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.
- The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified (Evidence B).
- Inhaled bronchodilators (particularly inhaled β_2-agonists with or without anticholinergics) and oral glucocorticosteroids are effective treatments for exacerbations of COPD (Evidence A).
- Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased sputum purulence) may benefit from antibiotic treatment (Evidence B).
- Noninvasive mechanical ventilation in exacerbations improves respiratory acidosis, increases pH, decreases the need for endotracheal intubation, and reduces Pa_{CO_2}, respiratory rate, severity of breathlessness, the length of hospital stay, and mortality (Evidence A).
- Medications and education to help prevent future exacerbations should be considered as part of follow-up, because exacerbations affect the quality of life and prognosis of patients with COPD.

Introduction. COPD is often associated with exacerbations of symptoms (197–201). An exacerbation of COPD is defined as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD" (202, 203). Exacerbations are categorized in terms of either clinical presentation (number of symptoms [199]) and/or heath care resources utilization (202). The impact of exacerbations is significant and a patient's symptoms and lung function may both take several weeks to recover to the baseline values (204).

The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution (205), but the cause of approximately one-third of severe exacerbations cannot be identified. The role of bacterial infections is controversial, but recent investigations have shown that at least 50% of patients have bacteria in high concentrations in their lower airways during exacerbations (206–208). Development of specific immune responses to the infecting bacterial strains, and the association of neutrophilic inflammation with bacterial exacerbations, also support the bacterial causation of a proportion of exacerbations (209–212).

Diagnosis and assessment of severity. MEDICAL HISTORY. Increased breathlessness, the main symptom of an exacerbation, is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color and/or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as tachycardia and tachypnea, malaise, insomnia, sleepiness, fatigue, depression,

and confusion. A decrease in exercise tolerance, fever, and/or new radiologic anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does prior history of chronic sputum production (199, 212).

ASSESSMENT OF SEVERITY. Assessment of the severity of an exacerbation is based on the patient's medical history before the exacerbation, preexisting comorbidities, symptoms, physical examination, arterial blood gas measurements, and other laboratory tests. Physicians should obtain the results of previous evaluations, where possible, to compare with the current clinical data. Specific information is required on the frequency and severity of attacks of breathlessness and cough, sputum volume and color, and limitation of daily activities. When available, prior arterial blood gas measurements are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. Thus, where possible, physicians should instruct their patients to bring the summary of their last evaluation when they come to the hospital with an exacerbation. In patients with stage IV COPD, the most important sign of a severe exacerbation is a change in the mental status of the patient and this signals a need for immediate evaluation in the hospital.

Spirometry and PEF. Even simple spirometric tests can be difficult for a sick patient to perform properly. These measurements are not accurate during an acute exacerbation; therefore, their routine use is not recommended.

Pulse oximetry and arterial blood gas measurement. Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. For patients that require hospitalization, measurement of arterial blood gases is important to assess the severity of an exacerbation. A $Pa_{O_2} <$ 8.0 kPa (60 mm Hg) and/or $Sa_{O_2} < 90\%$ with or without Pa_{CO_2} > 6.7 kPa (50 mm Hg) when breathing room air indicate respiratory failure. In addition, moderate to severe acidosis (pH < 7.36) plus hypercapnia ($Pa_{CO_2} >$ 6–8 kPa, 45–60 mm Hg) in a patient with respiratory failure is an indication for mechanical ventilation (196, 213).

Chest X-ray and ECG. Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an exacerbation, especially in advanced COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. A low systolic blood pressure and an inability to increase the Pa_{O_2} above 8.0 kPa (60 mm Hg) despite high-flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this together with the exacerbation.

Other laboratory tests. The complete blood count may identify polycythemia (hematocrit > 55%) or suggest bleeding. White blood cell counts are usually not very informative. The presence of purulent sputum during an exacerbation of symptoms is sufficient indication for starting empirical antibiotic treatment (33). *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* are the most common bacterial pathogens involved in COPD exacerbations. If an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and an antibiogram should be performed.

Biochemical test abnormalities can be associated with an exacerbation and include electrolyte disturbance(s) (e.g., hyponatremia, hypokalemia), poor glucose control, or metabolic acid–base disorder. These abnormalities can also be due to associated comorbid conditions.

DIFFERENTIAL DIAGNOSES. Patients with apparent exacerbations of COPD who do not respond to treatment (204, 214) should be reevaluated for other medical conditions that can aggravate symptoms or mimic COPD exacerbations (153), including pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and cardiac arrhythmia. Noncompliance with the prescribed medication regimen can also cause increased symptoms that may be confused with a true exacerbation. Elevated serum levels of brain-type natriuretic peptide, in conjunction with other clinical information, can identify patients with acute dyspnea secondary to congestive heart failure and enable them to be distinguished from patients with COPD exacerbations (215, 216).

Home management. There is increasing interest in home care for patients with end-stage COPD, although the exact criteria for this approach as opposed to hospital treatment remain uncertain and will vary by health care setting (217–220).

BRONCHODILATOR THERAPY. Home management of COPD exacerbations involves increasing the dose and/or frequency of existing short-acting bronchodilator therapy, preferably with a β_2-agonist (Evidence A). If not already used, an anticholinergic can be added until the symptoms improve (Evidence D).

GLUCOCORTICOSTEROIDS. Systemic glucocorticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time, improve lung function (FEV_1) and hypoxemia (Pa_{O_2}) (221–224) (Evidence A), and may reduce the risk of early relapse, treatment failure, and length of hospital stay (225). They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is less than 50% predicted. A dose of 30 to 40 mg prednisolone per day for 7 to 10 days is recommended (221, 222, 226).

ANTIBIOTICS. The use of antibiotics in the management of COPD exacerbations is discussed below in HOSPITAL MANAGEMENT.

Hospital management. The risk of dying of an exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support (227). Patients lacking these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Attempts at managing such patients entirely in the community have met with only limited success (228), but returning them to their homes with increased social support and a supervised medical care package after initial emergency room assessment has been much more successful (229). Savings on inpatient expenditures (230) offset the additional costs of maintaining a community-based COPD nursing team. However, detailed cost–benefit analyses of these approaches are awaited.

A range of criteria to consider for hospital assessment/admission for exacerbations of COPD are shown in Table 8. Some patients need immediate admission to an intensive care unit (ICU) (Table 9). Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment exist to identify and manage acute respiratory failure successfully.

The first actions when a patient reaches the emergency department are to provide supplemental oxygen therapy and to determine whether the exacerbation is life threatening. If so, the patient should be admitted to the ICU immediately. Otherwise, the patient may be managed in the emergency department or hospital (Table 10).

CONTROLLED OXYGEN THERAPY. Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient's hypoxemia. Adequate levels of oxygenation ($Pa_{O_2} >$ 8.0 kPa, 60 mm Hg, or $Sa_{O_2} > 90\%$) are easy to achieve in uncomplicated

TABLE 8. INDICATIONS FOR HOSPITAL ASSESSMENT OR ADMISSION FOR EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE*

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea, change in vital signs
- Severe underlying COPD
- Onset of new physical signs (e.g., cyanosis, peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbidities
- Frequent exacerbations
- Newly occurring arrhythmias
- Diagnostic uncertainty
- Older age
- Insufficient home support

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.
* Local resources need to be considered.

exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30 to 60 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks (high-flow devices) offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient (196).

BRONCHODILATOR THERAPY. Short-acting inhaled β_2-agonists are usually the preferred bronchodilators for treatment of exacerbations of COPD (153, 196, 231) (Evidence A). If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is controversial. Despite its widespread clinical use, the role of methylxanthines in the treatment of exacerbations of COPD remains controversial. Intravenous methylxanthines (theophylline or aminohylline) are currently considered second-line therapy, used when there is inadequate or insufficient response to short-acting bronchodilators (232–236) (Evidence B). Possible beneficial effects in terms of lung function and clinical endpoints are modest and inconsistent, whereas adverse effects are significantly increased (237, 238). There are no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (either β_2-agonists or anticholinergics) with or without inhaled glucocorticosteroids during an acute exacerbation.

GLUCOCORTICOSTEROIDS. Oral or intravenous glucocorticosteroids are recommended as an addition to other therapies in the hospital management of exacerbations of COPD (222, 223) (Evidence A). The exact dose that should be recommended is not known, but high doses are associated with a significant risk of side effects. Thirty to 40 mg of oral prednisolone daily for 7 to 10 days is effective and safe (Evidence C). Prolonged treatment does not result in greater efficacy and increases the risk of side effects.

TABLE 9. INDICATIONS FOR INTENSIVE CARE UNIT ADMISSION OF PATIENTS WITH EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE*

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia (Pa_{O_2} < 5.3 kPa, 40 mm Hg), and/or severe/worsening hypercapnia (Pa_{CO_2} > 8.0 kPa, 60 mm Hg), and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation
- Need for invasive mechanical ventilation
- Hemodynamic instability—need for vasopressors

* Local resources need to be considered.

TABLE 10. MANAGEMENT OF SEVERE BUT NOT LIFE-THREATENING EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN THE EMERGENCY DEPARTMENT OR THE HOSPITAL*

- Assess severity of symptoms, blood gases, chest X-ray
- Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30–60 min
- Bronchodilators:
  - Increase doses and/or frequency
  - Combine β_2-agonists and anticholinergics
  - Use spacers or air-driven nebulizers
  - Consider adding intravenous methylxanthines, if needed
- Add oral or intravenous glucocorticosteroids
- Consider antibiotics (oral or occasionally intravenous) when there are signs of bacterial infection
- Consider noninvasive mechanical ventilation
- At all times:
  - Monitor fluid balance and nutrition
  - Consider subcutaneous heparin
  - Identify and treat associated conditions (e.g., heart failure, arrhythmias)
  - Closely monitor condition of the patient

Data from Reference 226.
* Local resources need to be considered.

ANTIBIOTICS. On the basis of the current available evidence (196, 62), antibiotics should be given to the following individuals:

- Patients with exacerbations of COPD with the following three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence (Evidence B)
- Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (Evidence C)
- Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive) (Evidence B)

The infectious agents in COPD exacerbations can be viral or bacterial (140, 239). The predominant bacteria recovered from the lower airways of patients with COPD exacerbations are *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* (140, 206, 207, 240). So-called atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (240, 241), have been identified in patients with COPD exacerbations, but because of diagnostic limitations the true prevalence of these organisms is not known.

RESPIRATORY STIMULANTS. Respiratory stimulants are not recommended for acute respiratory failure (231). Doxapram, a nonspecific but relatively safe respiratory stimulant available in some countries as an intravenous formulation, should be used only when noninvasive intermittent ventilation is not available or not recommended (242).

VENTILATORY SUPPORT. The primary objectives of mechanical ventilatory support in patients with COPD exacerbations are to decrease mortality and morbidity and to relieve symptoms. Ventilatory support includes both noninvasive intermittent ventilation using either negative- or positive-pressure devices, and invasive (conventional) mechanical ventilation by orotracheal tube or tracheostomy.

Noninvasive mechanical ventilation. Noninvasive intermittent ventilation (NIV) has been studied in several randomized controlled trials in acute respiratory failure, consistently providing positive results, with success rates of 80 to 85% (182, 243–245). These studies provide evidence that NIV improves respiratory acidosis (increases pH, and decreases Pa_{CO_2}), and decreases respiratory rate, severity of breathlessness, and length of hospital stay (Evidence A). More importantly, mortality —or

its surrogate, intubation rate—is reduced by this intervention (245–248). However, NIV is not appropriate for all patients, as summarized in Table 11 (182).

Invasive mechanical ventilation. The indications for initiating invasive mechanical ventilation during exacerbations of COPD are shown in Table 12 and include failure of an initial trial of NIV (252). As experience is being gained with the generalized clinical use of NIV in COPD, several of the indications for invasive mechanical ventilation are being successfully treated with NIV.

The use of invasive ventilation in patients with end-stage COPD is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities. Major hazards include the risk of ventilator-acquired pneumonia (especially when multiresistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation. Contrary to some opinions, acute mortality among patients with COPD with respiratory failure is lower than mortality among patients ventilated for non-COPD causes (253). When possible, a clear statement of the patient's own treatment wishes—an advance directive or "living will"—makes these difficult decisions much easier to resolve.

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD and the best method (pressure support or a T-piece trial) remains a matter of debate (254–256). In patients with COPD who fail weaning trials, noninvasive ventilation facilitates extubation. It can also prevent reintubation in patients with extubation failure and may reduce mortality.

OTHER MEASURES. Further treatments that can be used in the hospital include the following: fluid administration (accurate monitoring of fluid balance is essential); nutrition (supplementary when needed); deep venous thrombosis prophylaxis (mechanical devices, heparins, etc.) in immobilized, polycythemic, or dehydrated patients with or without a history of thromboembolic disease; and sputum clearance (by stimulating coughing and low-volume forced expirations as in home management). Manual or mechanical chest percussion and postural drainage may be beneficial in patients with excessive sputum production or with lobar atelectasis.

Hospital discharge and follow-up. Insufficient clinical data exist to establish the optimal duration of hospitalization in individual patients who develop an exacerbation of COPD (197, 257, 258). Consensus and limited data support the discharge criteria listed in Table 13. Table 14 provides items to include in a follow-up assessment 4 to 6 weeks after discharge from the hospital. Thereafter, follow-up is the same as for patients with stable COPD, including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters (229). Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation of COPD, without increasing readmission rates (153, 259–261).

In patients who are hypoxemic during a COPD exacerbation, arterial blood gases and/or pulse oximetry should be evaluated before hospital discharge and in the following 3 months. If the patient remains hypoxemic, long-term supplemental oxygen therapy may be required.

Opportunities for prevention of future exacerbations should be reviewed before discharge, with particular attention to smoking cessation, current vaccination (influenza, pneumococcal vaccines), knowledge of current therapy including inhaler technique (32, 262, 263), and how to recognize symptoms of exacerbations. Pharmacotherapy known to reduce the number of exacerbations and hospitalizations and delay the time of first/next hospitalization, such as long-acting inhaled bronchodilators, inhaled glucocorticosteroids, and combination inhalers, should be specifically considered. Social problems should be discussed and principal caregivers identified if the patient has a significant persisting disability.

TABLE 11. INDICATIONS AND RELATIVE CONTRAINDICATIONS FOR NONINVASIVE INTERMITTENT VENTILATION

Selection criteria
- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Moderate to severe acidosis (pH $\leq$ 7.35) and/or hypercapnia (Pa_{CO_2} > 6.0 kPa, 45 mm Hg) (251)
- Respiratory frequency > 25 breaths/min

Exclusion criteria (any may be present)
- Respiratory arrest
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
- Change in mental status; uncooperative patient
- High aspiration risk
- Viscous or copious secretions
- Recent facial or gastroesophageal surgery
- Craniofacial trauma
- Fixed nasopharyngeal abnormalities
- Burns
- Extreme obesity

Data from References 196, 243, 249, and 250.

TABLE 12. INDICATIONS FOR INVASIVE MECHANICAL VENTILATION

- Unable to tolerate NIV or NIV failure (or exclusion criteria, *see* Table 11)
- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Respiratory frequency > 35 breaths/min
- Life-threatening hypoxemia
- Severe acidosis (pH < 7.25) and/or hypercapnia (Pa_{CO_2} > 8.0 kPa, 60 mm Hg)
- Respiratory arrest
- Worsening in mental status despite optimal therapy
- Cardiovascular complications (hypotension, shock)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)

Definition of abbreviation: NIV = noninvasive intermittent ventilation.

4. TRANSLATING GUIDELINE RECOMMENDATIONS TO THE CONTEXT OF (PRIMARY) CARE

KEY POINTS

- There is considerable evidence that management of COPD is generally not in accordance with current guidelines. Better dissemination of guidelines and their effective implementation in a variety of health care settings are urgently required.
- In many countries, primary care practitioners treat the vast majority of patients with COPD and may be actively involved in public health campaigns and in bringing messages about reducing exposure to risk factors to both patients and the public.
- Spirometric confirmation is a key component of the diagnosis of COPD and primary care practitioners should have access to high-quality spirometry.
- Older patients frequently have multiple chronic health conditions. Comorbidities can magnify the impact of COPD on a patient's health status, and can complicate the management of COPD.

TABLE 13. DISCHARGE CRITERIA FOR PATIENTS WITH EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- Inhaled β_2-agonist therapy is required no more frequently than every 4 h
- Patient, if previously ambulatory, is able to walk across room
- Patient is able to eat and sleep without frequent awakening by dyspnea
- Patient has been clinically stable for 12–24 h
- Arterial blood gases have been stable for 12–24 h
- Patient (or home caregiver) fully understands correct use of medications
- Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions)
- Patient, family, and physician are confident patient can manage successfully at home

The recommendations provided in sections 1 through 3 define—from a *disease* perspective—best practices in the diagnosis, monitoring, and treatment of COPD. However, (primary) medical care is based on an engagement with *patients*, and this engagement determines the success or failure of pursuing best practice. For this reason, medical practice requires a translation of disease-specific recommendations to the circumstances of individual patients—with regard to the local communities in which they live, and the health systems from which they receive medical care.

Diagnosis

In pursuing early diagnosis, a policy of identifying patients at high risk of COPD, followed by watchful surveillance of these patients, is advised.

Respiratory symptoms. Of the chronic symptoms characteristic of COPD (dyspnea, cough, sputum production), dyspnea is the symptom that interferes most with a patient's daily life and health status. When taking the medical history of the patient, it is therefore important to explore the impact of dyspnea and other symptoms on daily activities, work, and social activities, and provide treatment accordingly.

Spirometry. High-quality spirometry in primary care is possible (264, 265), provided that good skills training and an ongoing quality assurance program are provided. An alternative is to ensure that high-quality spirometry is available in the community—for example, within the primary care practice itself, in a primary care laboratory, or in a hospital setting, depending on the structure of the local health care system (266). Ongoing collaboration between primary care and respiratory care also helps assure quality control.

Comorbidities

Older patients frequently have multiple chronic health conditions and the severity of comorbid conditions and their impact on a patient's health status will vary between patients and in the same patient over time. Comorbidities for patients with COPD may include the following: other smoking-related diseases, such as ischemic heart disease and lung cancer; conditions that arise as a complication of a specific preexisting disease, such as pulmonary hypertension and consequent heart failure; coexisting chronic conditions with unrelated pathogenesis related to aging, such as bowel or prostate cancer, depression, diabetes mellitus, Parkinson's disease, dementia, and arthritis; or acute illnesses that may have a more severe impact in patients with a given chronic disease. For example, upper respiratory tract infections are the most frequent health problem in all age groups, but they may have a more severe impact or require different treatment in patients with COPD.

TABLE 14. ITEMS TO ASSESS AT FOLLOW-UP VISIT 4–6 WEEKS AFTER DISCHARGE FROM HOSPITAL FOR EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- Ability to cope in usual environment
- Measurement of FEV_1
- Reassessment of inhaler technique
- Understanding of recommended treatment regimen
- Need for long-term oxygen therapy and/or home nebulizer (for patients with stage IV, very severe COPD)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

Reducing Exposure to Risk Factors

Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants, including smoke from cooking over biomass-fueled fires, is an important goal to prevent the onset and progression of COPD. In many health care systems, primary care practitioners may be actively involved in public health campaigns and can play an important part in bringing messages about reducing exposure to risk factors to patients and the public. Primary care practitioners can also play a very important role in reinforcing the dangers of passive smoking and the importance of implementing smoke-free work environments.

Smoking cessation is the most effective intervention to reduce the risk of developing COPD, and simple smoking cessation advice from health care professionals has been shown to make patients more likely to stop smoking. Primary care practitioners often have many contacts with a patient over time, which provides the opportunity to discuss smoking cessation, enhance motivation for quitting, and identify the need for supportive pharmacologic treatment. It is very important to align the advice given by individual practitioners with public health campaigns to send a coherent message to the public.

Implementation of COPD Guidelines

GOLD national leaders play an essential role in the dissemination of information about prevention, early diagnosis, and management of COPD in health systems around the world. A major GOLD program activity that has helped to bring together health care teams at the local level is World COPD Day, held annually on the third Wednesday in November.* GOLD national leaders, often in concert with local physicians, nurses, and health care planners, have hosted many types of activities to raise awareness of COPD. WONCA (the World Organization of Family Doctors) is also an active collaborator in organizing World COPD Day activities. Increased participation of a wide variety of health care professionals in World COPD Day activities in many countries would help to increase awareness of COPD.

GOLD is a partner organization in the World Health Organization's GARD with the goal to raise awareness of the burden of chronic respiratory diseases in all countries of the world, and to disseminate and implement recommendations from international guidelines.

Although awareness and dissemination of guidelines are important goals, the actual implementation of a comprehensive care system in which to coordinate the management of COPD will be important to pursue. Evidence is increasing that a chronic disease management program for patients with COPD that incorporates a variety of interventions, includes pulmonary rehabilitation, and is implemented by primary care reduces hospital admissions and bed days. Key elements are patient participation and information sharing among health care providers (267).

*For further information on World COPD Day: http://www.goldcopd.org/WCDindex.asp.

Conflict of Interest Statement: K.F.R. has consulted, participated in advisory board meetings, and received lecture fees from AstraZeneca, Boehringer Ingelheim (BI), Chiesi Pharmaceuticals, Pfizer, Novartis, AltanaPharma, Merck, Sharp, and Dohme (MSD), and GlaxoSmithKline (GSK). The Department of Pulmonology, and thereby K.F.R. as head of the department, has received grants from AltanaPharma ($222,612), Novartis ($90,640), AstraZeneca ($113,155), Pfizer ($406,000), MSD ($118,000), Exhale Therapeutics ($90,000), BI ($90,000), Roche ($120,000), and GSK ($299,495) in the years 2001 until 2006. S.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.A. served as consultant in 2006 for Bayer Pharma ($2,000), Sanofi Aventis ($2,500), GSK ($2,000), BI ($2,000), and Sepracor ($3,000). He received lecture fees from BI/Pfizer for $3,000, Bayer Pharma for $2,500, and for symposia from BI for $1,500 and symposia from Kinetic Concepts, Inc. for $2,000. He also received industry-sponsored grants from Bayer Pharma in 2004–2005 for $30,000, C.R. Bard, Inc. for $60,000, BI for $50,000, NHLBI for $200,000, and GSK for $200,000. P.J.B. has received research funding, lecture fees, and has served on scientific advisory boards for GSK, AstraZeneca, BI, Novartis, AltanaPharma, and Pfizer. S.A.B. has served on advisory boards for GSK, Altana, Schering Plough, Merck, Novartis, Pfizer, and Sepracor. She has participated in COPD workshops funded by AstraZeneca and GSK; and is Scientific Director for the Burden of Obstructive Lung Disease (BOLD) initiative, which receives unrestricted educational grants to the Kaiser Permanente Center for Health Research from GSK, Pfizer, BI, AstraZeneca, AltanaPharma, Novartis, Merck, Chiesi, Schering Plough, and Sepracor. P.C. has spoken at scientific meetings for which he received honoraria (GSK, 2004—2006, $10,000; AstraZeneca, 2006, $3,000) and has served on advisory boards (GSK, 2004–2006, $15,000; AstraZeneca, 2004, $2,500; Pfizer, 2005–2006, $5,000). He has received industry-sponsored grants from GSK ($110,000) and AltanaPharma ($40,000). Y.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.J. has received fees for chairing or sitting on advisory boards of GSK, AstraZeneca, and Pfizer/BI, for a total value of $22,000 in the last 3 years. C.J. has also received fees for providing educational material and for giving lectures at industry-sponsored symposia to the value of $8,500 in the last 3 years. C.J. is a senior researcher in the Woolcock Institute of Medical Research, which participates in clinical trials sponsored by GSK, AstraZeneca, AltanaPharma (now NycoMed), and BI. The Institute is a member of a national collaborative research group, which is cofunded by government and industry. The major industry partners are GSK and Pharmaxis. R.R.-R. has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, BI, GSK, Laboratorios Dr Esteve SA, and Pfizer; consulted with several pharmaceutical companies with interests in the topics discussed in the present article (Almirall, AltanaPharma, AstraZeneca, BI, GSK, Laboratorios Dr. Esteve SA, Novartis, Pfizer, Viechi, and Zambon); serves on advisory boards for Almirall, BI, GSK, Novartis, Pfizer, Proctor and Gamble, and Viechi; has been sponsored for several clinical trials; and has received laboratory research support from AstraZeneca, BI, GSK, Laboratorios Dr Esteve SA, Pfizer, and Proctor and Gamble Ltd. C.v.W. has received speakers fees from Novartis, BI, AltanaPharma, and Pfizer, which have all been made available to the World Organization of Family Doctors (WONES). His department has received unrestricted research grants from GSK, BI, AstraZeneca, Novartis, Novo Nordisk, and Bayer. J.Z. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease

M J Doherty, R Mister, M G Pearson, P M A Calverley

Abstract

***Background*—Chronic cough is associated with an increased sensitivity to inhaled capsaicin in a number of conditions but there are no data for patients with more severe asthma or chronic obstructive pulmonary disease (COPD). Moreover, the relationships between the capsaicin response (expressed as the concentration of capsaicin provoking five coughs, C5), self-reported cough, and routine medication is not known.**

***Methods*—The cough response to capsaicin in 53 subjects with asthma, 56 subjects with COPD, and 96 healthy individuals was recorded and compared with a number of subjective measures of self-reported cough, measures of airway obstruction, and prescribed medication. In asthmatic subjects the relationships between the cough response to capsaicin and mean daily peak flow variability and non-specific bronchial hyperresponsiveness to histamine were also examined.**

***Results*—Subjects with asthma (median C5 = 62 mM) and COPD (median C5 = 31 mM) were similarly sensitive to capsaicin and both were more reactive than normal subjects (median C5 >500 mM). Capsaicin sensitivity was related to symptomatic cough as measured by the diary card score in both asthma and COPD (r = −0.38 and r = −0.44, respectively), but only in asthma and not COPD when measured using a visual analogue score (r = −0.32 and r = −0.05, respectively). Capsaicin sensitivity was independent of the degree of airway obstruction and in asthmatics was not related to PEF variability or PC_{20} for histamine. The response to capsaicin was not related to treatment with inhaled corticosteroids but was increased in those using anticholinergic agents in both conditions.**

***Conclusions*—These data suggest that an increased cough reflex, as measured by capsaicin responsiveness, is an important contributor to the presence of cough in asthma and COPD, rather than cough being simply secondary to excessive airway secretions. The lack of any relationship between capsaicin responsiveness and airflow limitation as measured by the FEV_1 suggests that the mechanisms producing cough are likely to be different from those causing airways obstruction, at least in patients with COPD.**

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Keywords: asthma; chronic obstructive pulmonary disease; cough reflex

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Chronic cough is one of the commonest symptoms of patients with persistent asthma[1] and may be the sole presenting feature of this disease.[2] Cough is frequently the first symptom reported by patients with chronic obstructive pulmonary disease (COPD)[3] and a cough productive of sputum is the cardinal feature of the subset of COPD patients defined as having chronic bronchitis.[4] However, sputum production is often scanty or absent as COPD progresses, yet cough remains a troublesome problem.[5]

Objective attempts to assess cough sensitivity have yielded conflicting results. When capsaicin, the pungent extract of red pepper, is inhaled it induces cough reproducibly without tachyphylaxis.[6] Patients with asthma have an increased sensitivity to capsaicin which is most marked in those who complain of cough.[7] When tested with citric acid, patients with COPD also have an increased cough response but this has not been reported with capsaicin.[7 8]

These differences could reflect the use of different tussive agents, differing patterns of symptoms, or differences in disease severity. Unfortunately, there are few specific data on spirometry or other symptoms available from the original capsaicin study which examined only 11 patients with COPD.[7] We hypothesised that the presence of chronic airflow limitation, whether due to asthma or COPD, would be associated with an increased capsaicin cough response, that the cough response would be related to the degree of airflow obstruction, and that the sensitivity to capsaicin would be altered by changing airway calibre. Moreover, we anticipated that there would a relationship between the capsaicin cough threshold and the perceived severity of the cough.

In the absence of an agreed symptomatic measure of cough severity, we have compared several methods of assessing cough as a symptom to the capsaicin response measured in groups of stable chronic asthmatic and COPD patients and have compared the objective data with our previously determined normal range of capsaicin responsiveness.

Methods

SUBJECTS

We recruited 53 patients with chronic asthma and 56 with COPD from our outpatient clinics. All the asthmatic patients met the conventional diagnostic criteria,[9] as did those with COPD[10] (table 1). The presence of a persistent cough was not necessary for inclusion in the study. All patients were clinically stable and any patient with a history of respiratory tract infection in the preceding four weeks, symptoms or investigations suggestive of oesophageal reflux,

Table 1 Demographic features, medication, and physiology of subjects studied

	Normal subjects	*Asthma*	*COPD*
No. of subjects	96	53	57
Median (range) age (years)	38 (20–65)	51 (22–73)	65 (45–88)
Sex (% male)	34	62	75
Smoking habits (%)			
Current smokers	17	17	40
Ex-smokers	20	40	60
Non-smokers	63	43	0
Drug treatment (%)			
β agonists	0	100	100
Anticholinergics	0	21	83
Theophylline	0	8	19
Inhaled corticosteroids	0	100	35
Lung function			
Mean (SE) FEV_1 (l)	3.7 (0.48)	2.1 (0.12)	1.1 (0.1)
Mean (SE) FVC (l)	4.4 (0.62)	3.4 (0.16)	2.6 (0.1)
% Predicted FEV_1 (SE)	107 (14)	71 (3)	42 (2)
Mean (SE) PEF variability (%)	—	15.9 (1.2) (n=53)	17.0 (1.8) (n=18)
Mean (SE) PC_{20} (mg/ml)	—	1.9 (0.46) (n=43)	—

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow; PC_{20} = concentration of histamine provoking a fall in FEV_1 of 20% or more.
Values are numbers of subjects except when otherwise stated.

subjects taking angiotensin converting enzyme inhibitors, or those less than 18 years of age were excluded, although there was no upper age limit. No patient had clinical or radiographic features suggestive of co-existing bronchiectasis. We excluded patients with a history of allergic rhinitis, post nasal drip, and those being treated for nasal symptoms. The data were compared with those derived from our normal subject population recruited from hospital staff, free from respiratory disease, who denied cough and were not receiving any medication. All subjects gave written informed consent to the study which was approved by our institutional ethical committee.

PROCEDURES

Subjects omitted short acting inhaled β agonists and anticholinergic agents for six hours before attendance and longer acting drugs such as oral theophylline or inhaled long acting β agonists for 12 hours on all test days. All subjects underwent the following tests.

Spirometry

Spirometric parameters were recorded with a wedge spirometer (Vitalograph, Maidenhead, Berkshire, UK) and the best forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) traces from three technically satisfactory attempts were used. Data are expressed as percentage predicted values.[11]

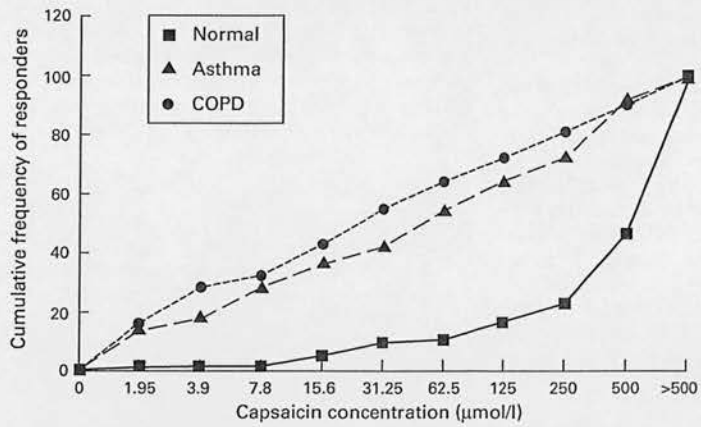

Figure 1 Comparison of the cumulative frequency at which subjects reached the C5 response for asthma and for subjects with COPD compared with normal subjects.

Capsaicin cough challenge

Capsaicin (Sigma Chemical Co, St Louis, Missouri, USA) was dissolved in absolute ethanol to make a stock solution of 10^{-2} M which was further diluted with 0.9% saline to produce nine doubling concentrations from 2 to 500 μM. Doses were administered from an Acorn nebuliser powered from a dosimeter calibrated to deliver 0.009 ml in each inhalation at a maximum flow rate of 0.75 l/s and a mass median particle diameter of 5.2 μm. Subjects were asked to take a single slow inhalation from the dosimeter beginning with saline control and then, with a minimum of 30 second intervals, increasing strengths of capsaicin until a given inhalation caused five coughs (C5). This dose was repeated to ensure that a reproducible C5 response had been attained and, if so, that the value was recorded as the patient's value (C5 capsaicin).

COPD: additional tests

Subjects with COPD then completed the following additional tests:

(1) Diary cards: these were completed at home over a two week period during which the subject recorded symptom scores or daily cough on a five point scale ranging from 1 = no cough to 5 = distressing cough most of the day. The score over the 14 day recording period was used to calculate the mean daily diary cough score. Peak expiratory flow (PEF) was self-recorded using a mini Wright peak flow meter four times a day in a standard fashion, the best of three measurements being taken. Peak flow variation for any particular day was taken as the difference between the highest and lowest peak flow divided by the highest measure. For patients with more than nine days of complete data the mean daily PEF variability was calculated.

(2) Hospital questionnaire: a detailed history of current respiratory medications was obtained with particular note of 'as needed' inhaled β agonists, regular inhaled anticholinergic agents, and inhaled corticosteroids (table 1). Sputum production was recorded as nil, occasional, or frequent. Symptoms of cough were recorded in a number of ways:

(a) the presence or absence of cough on most days;

(b) whether this cough was mild, moderate, or severe;

(c) using a 10 cm visual analogue scale (VAS) marked between no cough at one end and worst imaginable cough at the other end.

Further tests

After the above, patients with asthma and COPD were invited to perform further tests including lung volume measurement, histamine challenge tests, and the effect of bronchodilators on the C5 response. Histamine challenge tests were performed later the same day while lung volume estimation and effect of bronchodilators were measured on separate

study days during the following three weeks. In those with asthma the subgroup studied depended solely on the patient's willingness to undergo these investigations. In those with COPD some patients were unable to take a further part as they were about to enrol in another clinical trial, and others were only willing to some of the extra tests. There was no difference in mean age, percentage predicted FEV_1, or median C5 response between the subgroups who underwent additional tests and their parent cohorts.

(1) Static lung volumes and flow-volume loops: 38 patients with asthma and 20 with COPD performed flow-volume loops and measurement of static lung volumes while seated using a rolling seal spirometer (PK Morgan Ltd) with standard criteria for an acceptable loop.[11] After coaching, each subject performed repeated loops until three technically satisfactory traces were obtained. The loop with the largest sum of FEV_1 and FVC was chosen and from this loop PEF, 25–75% forced expiratory flow (FEF_{25-75}), and peak inspiratory flow (PIF) were derived. Static lung volumes were measured using the helium dilution technique.

(2) Histamine challenge: 43 asthmatic patients performed histamine challenge testing 15 minutes after the capsaicin study, inhaling from a dosimeter in a standard fashion. The FEV_1 was recorded before the histamine challenge to ensure that there was no change from the pre-capsaicin baseline. The concentration of histamine provoking a fall in FEV_1 of 20% or more (PC_{20}) was calculated by linear interpolation from the logarithmic concentration response curve.

(3) Effect of changing airway calibre on the C5 response: 40 patients with asthma and 13 with COPD performed a capsaicin challenge test and spirometric measurements both before and 30 minutes after each 5 mg nebulised salbutamol, 500 μg nebulised ipratropium bromide, and 3 ml 0.9% saline. All solutions were given using a System 22 Acorn nebuliser on separate days at the same time of the day in random double blind order. For each disease group and for each solution the C5 and FEV_1 values before and after administration of the nebulised agents were compared. Twenty three asthmatics performed a capsaicin challenge both before and immediately after the histamine challenge so that, at the time of the second histamine challenge, their FEV_1 was reduced by at least 20% from baseline. The effects of bronchoconstriction were then studied by comparing the difference between the C5 before and after the histamine challenge test with the difference between each subject's C5 response before and after saline.

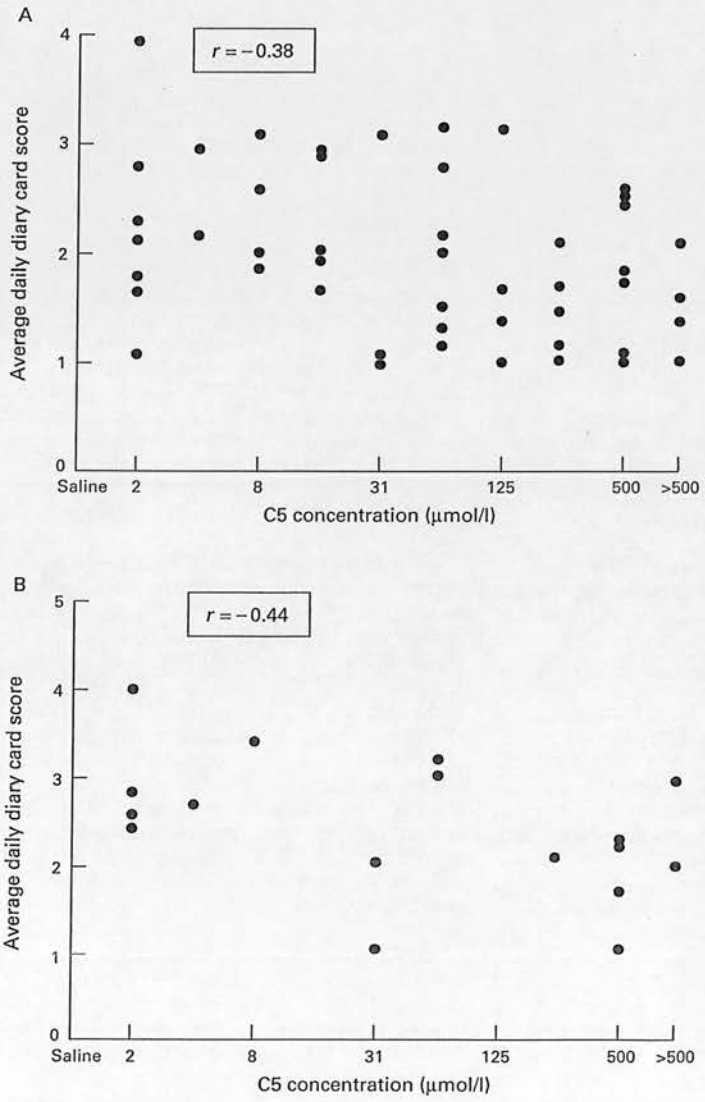

Figure 2 Scatter plots with Spearman correlation coefficients showing the relationship between self-reported cough measured using the daily diary card cough scores and capsaicin responsiveness (C5) for (A) asthma and (B) COPD.

STATISTICAL ANALYSIS

Median C5 values and the frequency distribution were used to describe the normal range in each disease group. These were then compared using the Kruskal Wallis test followed, if significant, by paired Mann-Whitney U tests between the groups.

The relationship between symptoms and sensitivity to capsaicin was examined in a number of ways. The average daily diary card cough score and the visual analogue score derived from the questionnaire were each related to the C5 of each subject using Spearman rank correlation coefficient within each disease group. Patients were grouped into those who did and those did not cough on most days and were then compared using Mann-Whitney U tests. Subjects were also divided into those who considered their cough to be mild, moderate, or severe and these groups were compared using the Kruskal Wallis test. Similarly, subjects with asthma and COPD were subdivided into those who rarely produced phlegm, those who occasionally produced phlegm, and those who usually produced phlegm and these groups were again compared using the Kruskal Wallis test. Lung function data are presented as mean (SE). The relationship between capsaicin sensitivity and

Table 2 Severity of self-reported cough in subjects with asthma and COPD using a variety of measures, and its relationship to regular treatment

	Asthma				COPD			
	n			*Median C5 (μM)*	*n*			*Median C5 (μM)*
Cough present	43	Cough most days	61%	16	57	Cough most days	81%	31
		No cough most days	39%	250 (p=0.015)		No cough most days	9%	31 (p=0.8)
Severity of cough	43	Mild	54%	125	57	Mild	31%	125
		Moderate	37%	63		Moderate	56%	16
		Severe	10%	16 (p=0.014)		Severe	12%	8 (p=0.1)
Sputum production	43	Usually	51%	16	57	Usually	56%	31
		Occasionally	28%	125		Occasionally	26%	31
		Rarely	21%	500 (p=0.014)		Rarely	16%	125 (p=0.8)
Anticholinergic therapy	53	Prescribed	21%	8	57	Prescribed	82%	31
		Not prescribed	79%	125 (p=0.02)		Not prescribed	18%	250 (p=0.03)
Inhaled corticosteroid therapy	53	Low dose	26%	93	57	Prescribed	35%	63
		Moderate dose	62%	63		Not prescribed	65%	31 (p=0.6)
		High dose	12%	125 (p=0.7)				

PC_{20} for histamine was examined using Spearman rank correlation coefficient as was that for the C5 response and lung function. Both pre and post nebuliser C5 and FEV_1 values as well as pre and post histamine C5 and FEV_1 values were compared using Mann-Whitney U tests.

Results

The clinical and physiological data at study entry are given in table 1. The patients with asthma were older than the normal subjects but younger than the patients with COPD ($p<0.001$) and almost 60% had been or were cigarette smokers. The median C5 was reduced in both asthma (62.5 μM) and COPD (31.2 μM) compared with the healthy controls (>500 μM, $p<0.001$, fig 1). There were no significant differences in the median or in the distribution of the C5 responses between the asthmatic and COPD patients.

ASTHMA SYMPTOMS AND LUNG FUNCTION

Diary card data for the 53 patients with asthma showed a mean (SE) daily cough score of 1.96 (0.1) which was inversely correlated with the C5 concentration ($r = -0.38$, $p<0.05$; fig 2A). Hospital questionnaire data using the VAS assessment of cough were correlated with the mean diary cough score in the 43 patients for whom both were available ($r = 0.40$, $p<0.05$). The VAS scores were more variable than the diary card scores, ranging from 0 to 8.5 cm, but they showed a similar weak correlation with the C5 values ($r = -0.32$, $p<0.05$).

The distribution of the responses to specific questions about the perception of cough are given in table 2. The presence of any cough, of a productive cough, and the patient's assessment of cough severity were all related to an increased cough response and to a lower percentage predicted FEV_1. However, overall there was no significant correlation between either the absolute FEV_1 or the percentage predicted FEV_1 and the measured C5 response (fig 3). The cough response was not related to whether or not subjects were current smokers or to the dose of inhaled corticosteroids taken. However, those patients using an inhaled anticholinergic drug did have a greater C5 sensitivity ($p = 0.002$; fig 3A). The C5 response of those patients not treated in this way was still significantly greater than that of the normal subjects.

COPD SYMPTOMS AND LUNG FUNCTION

Complete symptomatic data were available in only 19 cases, the remaining patients having been recruited into a study of inhaled corticosteroids where treatment changes might have affected the data. These patient groups did not differ significantly in their smoking habit, percentage predicted FEV_1, or median C5. They reported a higher daily cough score than the asthmatic subjects (2.36 (0.18) versus 1.96 (0.1)) but this difference was not significant. As for asthma, there was a correlation between the cough score and the mean C5 response ($r = -0.44$, $p<0.05$; fig 2B).

Data on the response of COPD patients to the cough questionnaire are given in table 2. Apart from a non-significant trend for the patients with 'severe' cough to have an increased sensitivity to capsaicin ($p = 0.1$), there were no associations between the presence or absence of symptoms and either C5 or FEV_1 (fig 4). Similarly, there was no association between the recorded C5 and current smoking status or the use of inhaled corticosteroids. However, those patients using inhaled anticholinergic treatment had an increased C5 response compared with those not so treated ($p<0.03$; fig 3C), the remaining subjects still having a greater C5 response than the healthy controls.

C5 AND THE EFFECTS OF RESTING LUNG FUNCTION AND ACUTE CHANGES IN AIRWAY CALIBRE

C5 values were independent of all the parameters derived from the flow-volume loop and of the static lung volumes. In patients with asthma C5 was unrelated to the diurnal PEF variability or to the baseline PC_{20} histamine. In the 40 patients tested before and after bronchodilators

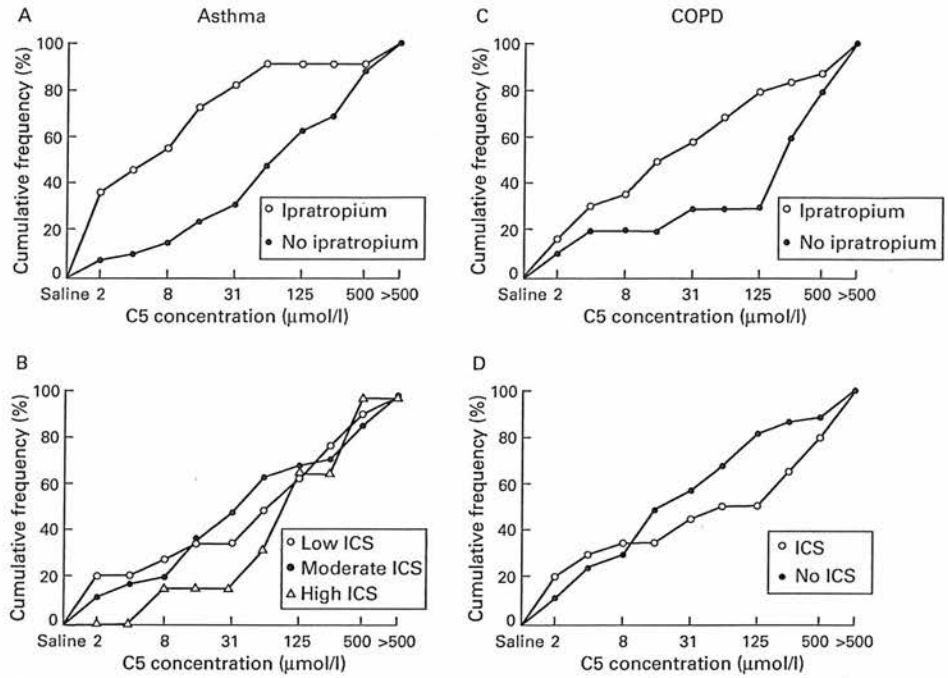

Figure 3 Comparison of the cumulative frequency at which subjects reached the C5 response by medication for both asthma and for COPD: (A) asthma: inhaled anticholinergics versus no inhaled anticholinergics; (B) asthma: low versus moderate versus high dose inhaled corticosteroids; (C) COPD: inhaled anticholinergics versus no inhaled anticholinergics; (D) COPD: inhaled corticosteroids versus no inhaled corticosteroids.

a mean increase in FEV_1 of 0.37 (0.04) l after salbutamol or 0.36 (0.04) l after ipratropium from a baseline of 2.07 (0.13) l did not change the median C5 response. Similarly, the median C5 values were unchanged in the 23 asthmatic patients measured before and after histamine challenge, despite a fall in FEV_1 of a mean of 0.6 (0.05) l from a baseline value of 2.1(0.12) l.

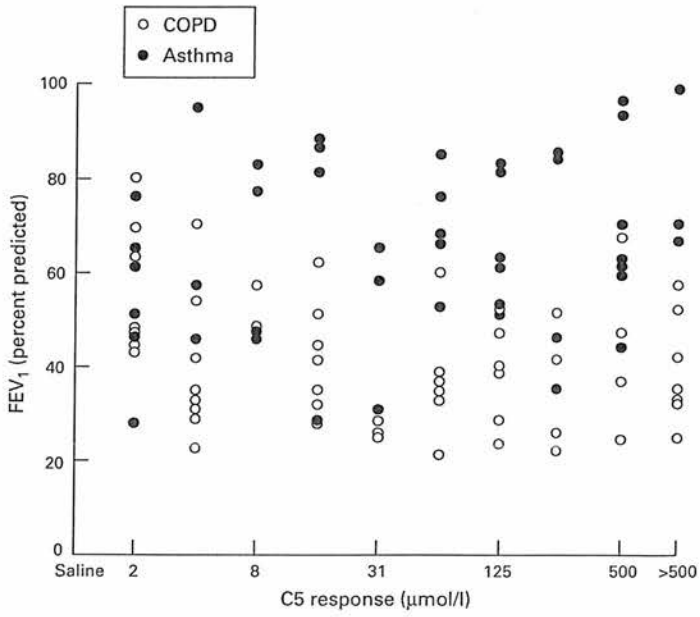

Figure 4 Scatter plot showing the relationship between C5 response and percentage predicted FEV_1 for both asthma and COPD

In the 13 patients with COPD tested before and after bronchodilators the FEV_1 rose from 1.2 (0.12) l to 1.37 (0.13) l after salbutamol and to 1.41 (0.14) l after ipratropium, but without a significant effect on the measured C5 response.

Discussion

The capsaicin cough challenge test is a simple and reproducible laboratory method for the assessment of cough susceptibility in a wide range of diseases.[7 12] It tests the afferent limb of the cough reflex which is thought to be mediated by rapidly adapting receptors within the airway wall. It can be increased by inhaling prostanoids in normal subjects[13] or by taking a thromboxane antagonist in patients with asthma.[14]

Studies in a range of conditions associated with chronic cough have shown an increased capsaicin sensitivity that falls with successful treatment, which can be achieved in two thirds of cases.[12] However, it is difficult to extrapolate data from these studies to patients with either asthma or COPD as the numbers studied, particularly in the latter group, are relatively small and data about lung function and bronchial reactivity are scanty. Our data in a large group of chronic persistent asthmatic subjects extend earlier observations in mild asthma that suggested that a reduced C5 cough threshold is a frequent finding which bears some relationship to the severity of the patient's symptoms. Other measures such as percentage predicted FEV_1 have recently been shown not to relate to the severity of cough in asthmatic subjects.[15]

Similar reductions in cough threshold were seen in patients with moderate to severe COPD, despite the significant differences in the baseline spirometric values and the different mechanisms producing the disease.[16]

Several methodological problems should be addressed. We performed our capsaicin challenge as described previously[7] with the additional feature of repeating the last concentration inhaled to confirm the C5 end point. We did not report the concentration producing two coughs (C2) as we have found this to be less reproducible than the C5 response in normal subjects and it does not add additional information. Others using similar methods have also found that C2 and C5 data yield similar information in other diseases.[18] As challenge test dosimeters are not identical, we have related changes in our patients to our laboratory's normal values rather than to those derived from the literature, although our normal range overlaps that described elsewhere. We used a fixed inspiratory flow rate to minimise differences in cough threshold between subjects.[17] In our laboratory we have found no evidence of age, sex, or smoking effects, unlike other reports.[18]

The reduced C5 in patients with chronic stable asthma was not surprising in view of the earlier reports in milder disease. A range of possible mechanisms involving different inflammatory mediators has been suggested to explain the enhanced C5 response.[13 19 20] However, given the heterogeneity of FEV_1 and PC_{20} of the asthmatic populations in which this has now been reported, it seems likely that increased cough susceptibility is either produced by very non-specific means or involves an entirely different pharmacological pathway from the mechanisms which determine the severity of airways reactivity or resting airway calibre. This has implications for the modification of cough as a symptom in asthma.

The reduction in C5 in the patients with COPD was unexpected as previous reports had suggested that the C5 response was normal in COPD and that the cough was perhaps related to increased sputum production and now increased responsiveness of laryngeal receptors.[21]

Studies in patients with chronic bronchitis or COPD where lung function data are available have examined less severe disease and/or a population diagnosed as having chronic sinus disease,[22] neither being representative of unselected COPD patients reported here. Our patients met the conventional diagnostic criteria for COPD, had limited bronchodilator reversibility and a history of past or current smoking, making it unlikely that there was a significant asthmatic element to their illness. In these patients we found no association between reported sputum production and either cough severity or C5 threshold.

Induced sputum studies have shown levels of pro-inflammatory cytokines in both asthma and COPD.[23 24] Persistent airway inflammation may contribute to the enhanced C5 response and merits further investigation.

The confounding effects of drug treatment or smoking are unlikely to explain our findings. Regular use of β agonists does not appear to modify the C5 response, despite earlier reports of benefit in cough induced in volunteers,[25] and our patients were asked to omit inhaled therapy before attendance. Short term use of oral corticosteroids and longer term use of inhaled corticosteroids are associated with changes in the frequency of symptomatic cough in COPD.[26] Specific data about the effect of these drugs on cough threshold are lacking. We found no relationship between smoking status and C5, neither did the regular use of β agonists or inhaled corticosteroids relate to the recorded response. Likewise, there were no differences in the symptom severity of cough, however assessed, and the presence of sputum production or use of inhaled corticosteroids. We found that the C5 cough threshold was significantly lower in both asthmatic and COPD patients taking regular inhaled ipratropium, although the patients not using these drugs were still more responsive than the control subjects. Whilst it is tempting to postulate that this may be a pharmacological effect, it is more likely to reflect selection of the more severe patients among the asthmatic group[9] and the widespread use of these drugs among COPD patients.[10] Indeed, anticholinergic agents have been shown to decrease rather than increase the nasal response to capsaicin.[27] Prospective studies of the capsaicin response before and after the introduction of anticholinergic treatment would be needed entirely to exclude this as an adverse reaction to treatment.

Whilst differences in the deposition of capsaicin to more central airway receptors might be hypothesised to explain some of the apparent similarities in asthmatic and COPD patients, the absence of any relationship between C5 and the severity of airflow limitation is a pointer against this. None of the measures of airflow limitation were related to C5 in either disease. Moreover, the C5 was unaltered even when the airway calibre was varied acutely, suggesting that neither airflow limitation alone nor changes in capsaicin deposition explain the increased level of response in our patients with asthma or COPD. A similar lack of effect of smaller changes in airway calibre has been reported in normal subjects,[25] but our data confirm that this is true in established disease when baseline FEV_1 is reduced.

C5 was not related to the level of bronchial hyperreactivity or to the level of PEF variability over two weeks, providing further evidence that the mechanisms underlying cough production are not necessarily related to those determining airway calibre.

Unlike previous studies, our patients were not selected because of their complaint of cough[12 17] but were randomly drawn from our outpatient clinics as we did not wish to bias our data by patients self-selected by their perception of a subjective complaint. Most patients, whatever the diagnosis, rated their cough as being of either mild or moderate severity, but the capsaicin response did not distinguish between these subjective grades. Other

mechanisms may be important in milder disease, but this discrepancy is more likely to reflect the relative insensitivity of assessing cough from a single interview. Perceptions about coughing reported at the hospital visit were poorly related to severity as assessed from the diary card data. However, patients with the most troublesome cough did have significantly lower C5 responses. In general, the agreement between symptom severity and the C5 response was somewhat better in the asthmatic subjects than in those with COPD. We should be cautious in interpreting group data showing symptomatic and C5 improvements with treatment in these diseases as the subjective and objective measurements may not necessarily change in the same way in an individual. This is in contrast to other forms of chronic cough such as that induced by ACE inhibitors where symptom severity and C5 are in good agreement in the individual before and after withdrawal of the drug.[28]

Our data show that a reduced cough threshold is a frequent finding in airways disease, whether associated with asthma or COPD. Reliance on one measure of self-reported coughing can be difficult to interpret, particularly in COPD. Use of the capsaicin challenge gives objective information about cough susceptibility which may prove more discriminatory than just questioning about the presence or absence of cough or sputum production. The relative role of this mechanism and its relationship to the effects of other agents such as citric acid or low Cl^- as the disease progresses merits further study. The mechanisms producing increased capsaicin responsiveness, whether inflammatory or mediator driven, also require further exploration, particularly in patients with COPD where an abnormal cough threshold appears to be relatively common.

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Qualitative aspects of breathlessness in health and disease

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ABSTRACT

Background: Patients with respiratory disease use many different expressions to describe the sensation they experience as breathlessness. Although previous analyses have identified multiple dimensions of breathlessness, there is little agreement about their number and nature. This study has applied a novel approach, principal component analysis (PCA), to understanding descriptions of breathlessness in health and disease and extracting representative components.

Methods: 202 patients (asthma n = 60, chronic obstructive pulmonary disease n = 65, interstitial lung disease n = 41, idiopathic hyperventilation n = 36) and 30 healthy volunteers were studied. All subjects performed spirometry and gave binary responses to 45 descriptions recalling their experience of breathlessness at the end of exercise; patients repeated this for resting breathlessness. PCA identified response patterns in the questionnaire data and extracted discriminatory components. Component scores were calculated for each individual using the regression method.

Results: PCA identified six distinct components of breathlessness on exercise, explaining 62.8% of the variance: (1) air hunger, (2) affective, (3) nociceptive, (4) regulation, (5) attention and (6) miscellaneous qualities. Rest components explaining 63.1% of variance were (1) affective, (2) air hunger, (3) nociceptive, (4) wheeze, (5) regulation and (6) miscellaneous. Components identified on exercise differed significantly between disease groups and controls and were related to percentage predicted forced vital capacity.

Conclusion: This analysis suggests that air hunger is the dominant sensation during exercise, while affective distress characterises resting breathlessness in patients with a range of respiratory disorders including idiopathic hyperventilation where lung mechanics are normal. This suggests that common mechanisms operate in qualitative aspects of breathlessness.

Breathlessness is one of the most frequent and distressing symptoms experienced by patients with lung disease and is usually defined as an uncomfortable awareness of breathing.[1] Healthy subjects also experience breathlessness during exercise and this may be characterised as physiologically appropriate breathlessness. The clinical assessment of breathlessness usually focuses on the degree or intensity of the symptom, and much scientific effort has been dedicated to understanding the factors that determine the severity of breathlessness.[2–4] Less attention has been paid to the quality of the sensation and whether this differs between conditions, although some believe this is the case.[5 6]

Patients with a respiratory disease use a wide variety of terms to describe the sensations experienced when they become breathless. These sensations cannot be assessed objectively[7] and, instead, representative verbal descriptors have been identified.[8] Although previous analyses in health[9 10] and disease[5 8 11–13] have identified clusters of these descriptors (using cluster analysis), there is little consistency in their number and nature and, moreover, they are not sufficiently robust to aid in differential diagnosis.

An alternative approach to cluster analysis is to use principal component analysis (PCA) which uncovers the latent structure (dimensions) of a set of variables—in this case, breathlessness descriptors—by identifying important sources of variation. PCA has the advantage that it does not assume that distinct groups of descriptions exist; a variable can appear in two separate components and components can be allowed to correlate with each other. Differences in the interpretation of descriptions by subjects can therefore be accommodated while also avoiding the constraint of generating a hierarchic classification. This has been shown to be a useful technique for identifying patterns of respiratory symptoms in children[14] but only one study has applied PCA to breathlessness, analysing a mixture of symptoms and qualitative descriptors in an attempt to identify subjects with medically unexplained breathlessness.[15]

We have applied PCA to the responses of healthy volunteers and discrete patient groups to descriptions of breathlessness. We chose our patient groups to represent a range of mechanical abnormalities, both fixed and variable, that are applied to the respiratory system, and our principal focus was on the recall of the sensation of breathlessness perceived at the end of exercise. We hypothesised that the quality of breathlessness would differ between healthy volunteers and patients with respiratory disease and would also differ between breathlessness recalled at end of exercise and that experienced at rest, although this analysis was confined to patients with disease where this might occur. Finally, we have explored the relationship between the components of breathlessness and spirometry as an objective measurement of altered lung mechanics.

METHODS

Patients

Consecutive patients attending the outpatient clinic and the respiratory function laboratory of University Hospital Aintree were recruited. Healthy control subjects of a similar age were identified from hospital staff and relatives of patients.

Diagnoses were confirmed by review of the medical records and subjects categorised as chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease (ILD) and idiopathic hyperventilation (IHV) when they unequivocally met the established diagnostic criteria for these disorders[16–18] (see online supplement for details). Patients with more than one condition causing breathlessness were excluded.

All patients performed spirometry using a wedge bellows spirometer (Vitalograph-R, Vitalograph Ltd, Buckinghamshire, UK); control subjects were tested using an ultrasonic portable spirometer (Easy One, NDD Medical Technologies, Zurich, Switzerland). The best of three manoeuvres has been reported, measured to ATS/ERS standards.[19]

Questionnaire

A questionnaire comprising 45 short phrases describing breathlessness and previously shown to be valid and reliable[8] was completed by each subject twice. Patients were asked to think about how they felt when breathless at rest and to respond to all items (yes or no). Subjects were then asked to think about how they felt when breathless at end of exercise and to respond to the same set of items; healthy subjects completed only the exercise section. Unless they requested assistance, subjects were left alone and given as much time as they needed to complete the questionnaires.

Data analysis

All statistical analyses were performed using SPSS 13.0 (SPSS Inc, Chicago, Illinois, USA). PCA was used to identify response patterns in the questionnaire data both at rest and on exercise.[20] PCA is an exploratory technique for investigating patterns within a set of variables—in the current analysis, responses to a series of descriptions of breathlessness. The large numbers of responses can be reduced to a much smaller number of representative components based on the covariance among responses. If subsets of symptoms are correlated, this suggests they are measuring aspects of a common underlying process; several components may suggest a series of underlying processes. The steps involved in each analysis were as follows.

Item selection

Redundant questions were removed (ie, question responses with partial correlation coefficients >0.4 to other question responses). To maximise the informative content of the analysis, items that correlated with several other variables were removed first.

Component extraction

PCA was used to generate the components and the numbers of components for analysis were selected based on the Eigenvalues and scree plots.

Rotation

Component rotation is used to improve the interpretability of the results. An oblique rotation was chosen (Promax), assuming that the components of breathlessness were unlikely to be entirely independent of one another. The loading of the items onto each component is a measure of the relationship between that item and the component—the greater the loading, the purer a measure of that component the item is. Only items with the conventional loading of 0.4 and above were interpreted.

Component scores

For each subject included in the analysis it is possible to calculate scores for the individual components. These scores are derived from the subjects' responses to the items comprising each component and their loadings. Scores were calculated using the regression method; for each component the scores were standardised; each has a mean value of 0 and a standard deviation of 1. The scores indicate the relative importance of that qualitative component of breathlessness for each individual, not the intensity of breathlessness.

In addition, we applied agglomerative hierarchical cluster analysis (using the squared Euclidean distance as the dissimilarity measure) to the data set in order to compare the components with the clusters formed. This allowed comparison of our result with those previously generated using this questionnaire.[8]

There are no available criteria against which the solution in a PCA can be tested. However, the solution can be assessed for face validity of the components and by examining the relationships between the component scores generated and other available variables. We therefore examined whether diagnostic grouping and also spirometric abnormality significantly predicted component scores using multivariate analysis of variance (MANOVA). If the predictor terms were significantly related to the component scores (according to the Pillai test), then individual associations between predictors and components were examined using specific tests. As patients with different conditions will inevitably have differences in spirometry, the relationships between component scores and spirometry were adjusted for differences due to diagnosis.

RESULTS

A total of 310 patients and 35 normal subjects were approached to fill in the questionnaire; 234 patients and 35 normal subjects agreed to take part in the study. Thirty-two patients and 5 healthy volunteers were excluded, leaving 202 patients and 30 normal subjects for analysis. The main reasons for exclusion were: inconsistency in answering the repeat questions (>1 item answered differently) and failure to give a response to more than 5 questions. Patient characteristics, diagnoses and spirometric data are shown in table 1.

Component extraction

Exercise

For the analysis, data were pooled for the control and patient groups. Thirty-five items were included in the PCA (Kaiser-Meyer-Olkin measure of sampling adequacy 0.95, Bartlett's test of sphericity <0.001); item selection is summarised in table E1 in the online supplement. Six components with Eigenvalues >1 were identified (fig E1 in the online supplement), explaining 62.8% of the variance in the data. The main break in the scree plot was after one component as the first component explained the majority of the variance; however, the inclusion of the additional five components added a further 20% to the variance explained. The questionnaire items loading >0.4 onto each component are shown in table 2, along with the proportion of variance explained by each component. We named each component based on the theme represented by the most strongly loading items. For the descriptions of breathlessness on exercise, the dominant component was air hunger (items referring to a need for more air). The other independent components explaining smaller percentages of the total variance were (in order of magnitude): affective; items suggesting

Table 1 Characteristics of study subjects

Diagnosis	Gender	Mean age (years)	FEV_1% predicted	FVC% predicted	FEV_1/FVC ratio
Asthma (n = 60)	19M/41F	48.2 (15.4)	80.6 (26.6)	93.3 (26.7)	71.6 (12.1)
COPD (n = 65)	32M/33F	67.9 (9.2)	42.0 (30.5–56.5)*	78.3 (21.3)	40.2 (33.0–55.5)*
Interstitial lung disease (n = 41)	24M/17F	68.7 (9.9)	72.0 (18.9)	73.2 (20.2)	78.1 (8.4)
Idiopathic hyperventilation (n = 36)	8M/28F	53.7 (15.2)	93.0 (88.0–104.5)*	99.3 (14.4)	79.1 (7.6)
Healthy controls (n = 30)	11M/19F	53.8 (12.7)	106.5 (16.0)	113.3 (17.2)	77.2 (6.3)

Data are mean (SD) except for *median (interquartile range).
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

emotional distress, nociceptive; descriptions of unpleasant sensations, regulation; perceptions of inappropriately regulated breathing, attention; subjective awareness of breathing; and miscellaneous descriptions including sighing, air not tasting right and breath stopping. Several descriptions featured in more than one component (eg, air hunger loaded onto the air hunger and affective components).

Rest

Only data for the patients was used for this analysis. Thirty-four items were included in the PCA (Kaiser-Meyer-Olkin measure of sampling adequacy 0.92, Bartlett test of sphericity <0.001); item selection is summarised in table E2 in the online supplement. Again, six components with Eigenvalues >1 were identified (fig E2 in the online supplement), explaining 63.1% of

Table 2 Pattern matrix: item loadings on exercise for patients and controls, six component solution with Promax rotation

	Component loadings					
Components (% variance) items	1	2	3	4	5	6
(1) Air hunger component (42.6%)						
Cannot breathe deeply enough	0.86					
Need to take a deeper breath	0.83					
Breathing too shallow	0.77					
Not satisfied by my breathing	0.67					
Can't get enough air into my chest	0.67					
Cannot breathe enough	0.67					
(2) Affective component (5.8%)						
Desperate for breath		0.89				
Suffocating		0.86				
Gasping for breath		0.74				
Hunger for more air	0.52	0.68				
Fighting for breath		0.65				
(3) Nociceptive component (4.6%)						
Chest aches			0.82			
Chest feels tight			0.77			
Raw sensation in chest			0.74			
Wheezy			0.65			
Raw sensation in throat			0.50			
Winded in my chest			0.41			
(4) Regulation component (3.7%)						
Breathing is too deep				0.88		
Breathing is too fast				0.68		
Breathing is too heavy				0.63		
Breathing feels unpleasant				0.50		
Can't control my breathing				0.41		
(5) Attention component (3.1%)						
Puffed					0.71	
Aware of my breathing					0.66	
Need breath	0.47				0.53	
Short of breath					0.52	
Out of breath					0.49	
(6) Miscellaneous component (3.0%)						
Want to sigh					0.42	0.61
Air does not taste right		0.48				0.59
My breath stops		0.47				0.55

The magnitude of the component loadings represents how good each item is as an indicator of the component.
All items shown load >0.40 onto PCA components.

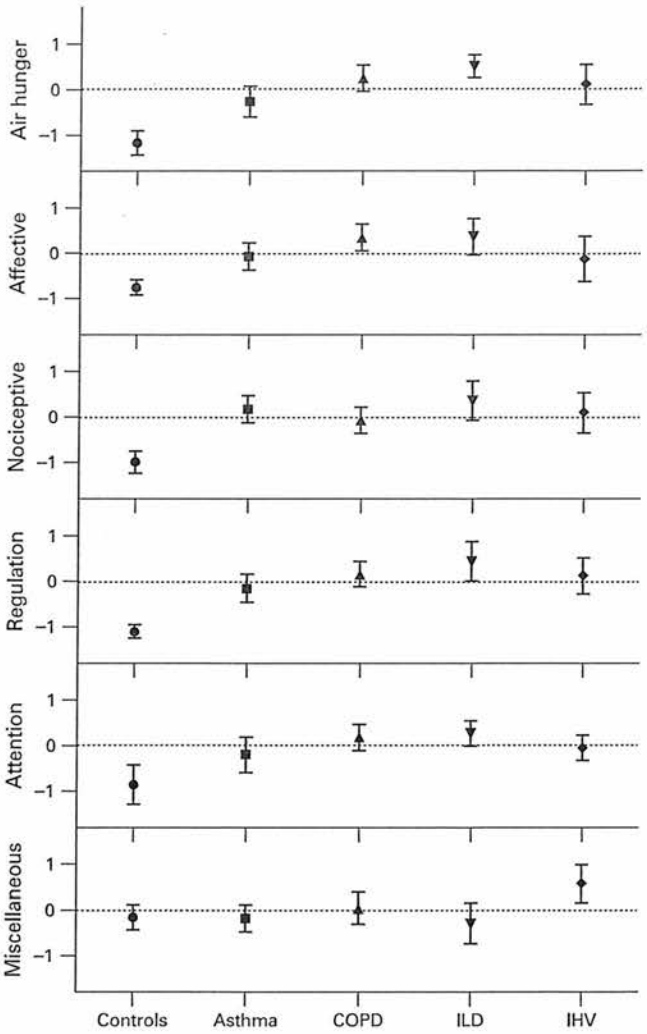

Figure 1 Comparison of diagnostic groups for each component score on exercise. Mean and 95% confidence intervals are shown. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IHV, idiopathic hyperventilation.

the variance in the descriptions. The questionnaire item loadings are shown in table E3 in the online supplement. The items in the components were either identical to or synonymous with those for exercise: (1) affective, (2) air hunger, (3) nociceptive, (4) wheeze, (5) regulation and (6) miscellaneous descriptions. An additional component representing wheeze emerged, but the attention component was not present. At rest the dominant component was the affective one.

To assess whether the absence of controls from the analysis had produced this change in the components and the variance explained, the PCA was repeated on the exercise data without the healthy volunteers. This confirmed that the air hunger component still explained most of the variance (see table E4 in online supplement) and the nociceptive items split into two components.

Agglomerative hierarchical cluster analysis

The exercise pooled control and patient data were analysed using all 45 descriptions. This generated a complex dendrogram. Using the criteria as previously applied by Elliott *et al*[8] (squared Euclidean distance of 12.5), 17 clusters of descriptions were produced (fig E3 and table E5 in online supplement). At a Euclidean distance of 17.5 the cluster analysis gave six clusters. However, these did not seem to represent coherent themes—for example, the items in the air hunger and affective components appeared in a single cluster.

Breathlessness component scores in health and disease

Using the scores generated by the regression method, we were able to examine the validity of the components by assessing their ability to discriminate between control subjects and those with respiratory disease. Gender and age had no significant effect on any component score but, for the regulation component, there was a trend towards a significant gender difference at rest ($p = 0.06$) and on exercise ($p = 0.09$).

Exercise component scores

The diagnostic category significantly influenced the component score for all six exercise components (air hunger $p<0.001$, affective $p<0.001$, nociceptive $p<0.001$, regulation $p<0.001$, attention $p = 0.001$ and miscellaneous $p = 0.008$). Post hoc analyses (Bonferroni correction for multiple comparisons) suggested that, compared with controls, the value of the component scores was greater for the air hunger component ($p<0.001$ for all diagnoses), the regulation component ($p<0.001$ for all diagnoses) and the nociceptive component ($p<0.001$ for all diagnoses) (fig 1). There were also significantly different scores compared with controls for the affective component in asthma, COPD and ILD ($p = 0.005$, $p<0.001$ and $p<0.001$, respectively) but not IHV ($p = 0.125$); a similar pattern occurred for the attentive component (COPD $p<0.001$, ILD $p = 0.001$, and borderline significance for IHV $p = 0.06$ and asthma $p = 0.082$). In contrast, the miscellaneous component was significantly higher in IHV than asthma or ILD ($p = 0.03$ and $p = 0.007$, respectively).

Rest component scores

The only significant difference between the diagnostic groups at rest was for the affective component ($p = 0.04$). Post hoc analysis suggested a higher score in subjects with COPD than in those with asthma ($p = 0.04$, fig E4 in online supplement).

Breathlessness component scores and spirometry

MANOVA models (exertion and rest) were generated with component scores as the dependant variables and spirometry as predictors. The ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) was used to indicate airflow obstruction and FVC percentage predicted was used as a marker of volume change. All models were adjusted for age, gender and diagnosis.

In the multivariate model for exercise, FVC percentage predicted independently predicted all the breathlessness component scores except for the miscellaneous component (air hunger $p<0.001$, affective $p<0.001$, nociceptive $p = 0.001$, regulation $p<0.001$ and attention $p = 0.02$). Post hoc analyses suggested that FVC percentage predicted was significantly related to air hunger, affective and nociceptive components, independent of diagnosis (table 3). The FEV_1/FVC ratio was not significant in the model ($p = 0.37$).

At rest, the FEV_1/FVC ratio and FVC percentage predicted did not significantly influence the component scores when the model was adjusted for age, gender and diagnosis.

Table 3 Post hoc analyses for variables significantly predicting breathlessness components on exercise in MANOVA

Components	Independent variables	p Values
Exercise air hunger	FVC (% predicted) Diagnosis	0.02, <0.001
Exercise affective	FVC (% predicted)	0.004
Exercise nociceptive	FVC (% predicted) Diagnosis	0.02, 0.001
Exercise regulation	Diagnosis	<0.001
Exercise attentive	Diagnosis	<0.001
Exercise miscellaneous	–	–

Diagnosis reflects the independent impact of a specific diagnostic category.
FVC, forced vital capacity.

DISCUSSION

Although breathlessness is a cardinal symptom in respiratory disease, relatively little attention has been paid to its qualitative aspects. This reflects the difficulty in developing consistent themes from the range of attributes associated with this symptom. The replication of cluster analysis results in different patient groups has seldom been shown, while the resulting dendrograms are difficult to interpret. This is the first study to demonstrate that PCA can be successfully applied as an alternative to this approach and can identify different components of breathlessness experienced both at rest and end of exercise. The variation in the description of breathlessness at end of exercise was dominated by a single component relating to air hunger whereas, at rest, descriptions with emotional connotations (affective component) were the most important discriminators. Much smaller contributions were made by other components representing nociceptive sensations, attributes related to how breathing is regulated, wheeziness and the attention paid to the act of breathing. In general, the association of these variables and the diagnosis was closer on exercise than in the resting data. Gender and age had no significant effect on any component score, suggesting that the differences seen in perceived intensity of exertional breathlessness in older women[21] are not associated with differences in quality of breathlessness.

To aid comparison with published data, we used the same list of descriptions of breathlessness as those reported by Elliott *et al*.[8] Like them, we obtained a relatively complex dendrogram with a large number of clusters. This implies that breathlessness is a complicated sensation with a large number of dimensions, but we were not able to replicate the clusters formed and these differed significantly from the components indicated by the PCA. In contrast, PCA produced a smaller number of components with good face validity. When a simpler structure was derived from the cluster analysis (six clusters) it was apparent that the items in the air hunger and affective components from the PCA formed a single cluster (ie, were not discriminated by this technique). Furthermore, the remaining clusters lacked consistent themes.

Although the terms used to describe each cluster and each component are arbitrary and can be debated, the patients clearly identified qualities of unsatisfied inspiration within the grouping "air hunger" as the dominant perception of breathlessness on exercise. By contrast, terms related to emotional distress, "affective" attributes, were the ones most characteristic of breathlessness perceived at rest, reflecting the frightening nature of this sensation previously identified by patients such as those with COPD.[22]

The validity of the PCA was confirmed by our analysis of the derived component scores. We found that exercise components clearly distinguished between breathlessness in health and disease, but there were few significant differences between the different conditions for both rest and exercise. However, there was a difference in the affective component scores between asthma and COPD which could reflect the reported prevalence of depression in COPD, which is itself associated with chronic breathlessness.[23 24]

The dominance of air hunger as the major quality of breathlessness on exercise, irrespective of the differences in the mechanical behaviour of the lungs and those reporting it, is initially surprising. This may reflect a common mechanism generating this sensation on exercise. Air hunger is equally induced by both hypercapnia and hypoxia in health[25] but is also experienced by ventilated quadriplegic subjects,[26] supporting a model in which air hunger is mediated, at least in part, via the chemoreceptors and is independent of respiratory muscle contraction; this has been confirmed by studies in paralysed non-sedated volunteers.[27] However, the adequacy of pulmonary inflation is also important in both inducing and relieving air hunger,[28] suggesting that the sensation results from a balance between chemoreceptor and mechanoreceptor inputs.[29] In disease, the factors modulating this interaction are complex. We speculate that mechanical limitation at end of exercise is a possible unifying explanation for the dominance of air hunger across our disease groups. Patients with significant airflow obstruction who report breathlessness show dynamic hyperinflation of their end-expiratory lung volume during exercise.[30] Moreover, the degree of breathlessness increases significantly as the end-inspiratory lung volume approaches the inspiratory reserve volume.[29 31] A similar situation may apply in ILD where the absolute inspiratory reserve volume is reduced.[32] Although patients with IHV do not have any mechanical limitation to breathing at rest, they do show respiratory rather than cardiovascular limitation on exercise and the large tidal volume breathing they adopt at end of exercise is likely to encroach on the inspiratory reserve volume and generate a dissimilar sensation of unsatisfied inspiration.[33] This interpretation is in keeping with our limited physiological data which showed that FVC rather than FEV_1 was related to the sensation of breathlessness irrespective of the diagnosis. Thus, a common mechanism may explain why seemingly different diseases at rest produce qualitatively similar sensations.

Our study investigated respiratory diseases as a cause of breathlessness and omitted other conditions such as congestive heart failure where a mixture of cardiac and pulmonary abnormalities contribute directly or indirectly to dyspnoea. Our patient groups represent a spectrum of respiratory disease, all causing breathlessness but characterised by different mechanical abnormalities—the asthma and COPD groups representing variable and fixed airflow obstruction and the ILD group representing a purer form of elastic respiratory loading. Previous reports have not always included healthy controls in the same study as patients,[5 8 11] and have not studied subjects with IHV. The subjects with IHV acted as a "positive control" group—subjects with symptoms of breathlessness but with normal spirometry, transfer factor and resting lung volumes. Patients with IHV are often felt to have psychological problems underlying their breathlessness, but our data indicate that the sensation experienced is the same as in patients with structural lung disease. The association of air hunger as the dominant exercise-related symptom was not different from that where breathlessness was due to organic factors, nor was there any stronger attribution of breathlessness to factors associated with the affective or emotional components we identified—something which might be expected if psychological factors played a dominant role in this condition.

Our study has some limitations. We used a questionnaire developed by others to try and reduce variability between our datasets. However, the descriptions within this questionnaire are not strongly representative of the work or effort of breathing, an attribute previously described as being strongly related to breathlessness.[34] However, our main interest was to identify the qualitative dimensions of breathlessness rather than dimensions inextricably related to the intensity of respiratory drive such as work and effort. It also would have been interesting to establish objectively the exercise capacity of all the participants, but PCA requires a large number of subjects making this impractical, notwithstanding the difficulties in identifying a suitable standardised test for all the disease groups studied. The range of spirometric abnormalities in the selected patient groups should be sufficient to encompass a wide range of exercise performance. Finally, we related breathlessness to a specific point during exercise—namely, maximum exercise performance—and it is possible that mechanisms operating earlier in exercise may be associated with a different quality of respiratory sensation. However, given the number of individuals questioned, identifying a specific point to consider made it easier for them to focus on the wide range of attributes they were asked to classify.

Our data suggest that the qualitative experience of breathlessness involves a variety of unpleasant sensations which are shared by a range of respiratory conditions irrespective of their aetiology. Whether the same is true for other conditions where breathlessness limits exercise remains to be determined. We have not identified significant differences in the qualitative attributes of breathlessness which are disease-related, so the present clinical practice of quantifying the intensity of the sensation relative to the task which produces it appears to capture the important attributes of breathlessness.

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Qualitative aspects of breathlessness in health and disease

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The Effect of Oxygenation on Sleep Quality in Chronic Bronchitis and Emphysema[1,2]

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SUMMARY We recorded the electroencephalogram, electrooculogram, electromyogram, and ear oxygen saturation (Sa_{O_2}) during sleep in 20 patients with chronic bronchitis and emphysema, 13 of whom had a low arterial P_{O_2} and elevated P_{CO_2} ("blue and bloated") and 7 of whom had a relatively normal arterial P_{O_2} and P_{CO_2} ("pink and puffing"), and compared the findings in these patients with 9 healthy subjects of similar age. All subjects slept for 2 nights and there was no difference between the groups in the total sleep period. The patients had a lower stable Sa_{O_2} than the normal subjects, the "blue and bloated" patients having significantly more hypoxemic episodes during sleep ($p < 0.01$). Transient nocturnal hypoxemia was commonest during REM sleep in both patients and healthy subjects and its duration was not related to any sleep variable examined. The patients had significantly shorter periods of sleep between the episodes of brief arousal occurring during the night ($p < 0.02$). Six representative "blue and bloated" patients (mean FEV_1, 0.6 ± 0.2 L; mean Pa_{O_2}, 48 ± 7 mmHg; mean Pa_{CO_2}, 50 ± 6 mmHg) were studied for a further night receiving either air or oxygen on successive study nights. When breathing oxygen there were fewer hypoxemic episodes per night (mean, 3.7 breathing air; mean, 1.5 breathing oxygen) and the amount of sleep proper (Stages 2, 3, and 4) increased in 5 of 6 patients. Intervening wakefulness and drowsiness was reduced by oxygen, and the amount of time spent in REM sleep increased to 17% of total sleep. The total sleep period and distribution of sleep stages in the "blue and bloated" patients breathing oxygen resembled that seen in normal subjects rather than in the "pink and puffing" patients with a similar degree of airway obstruction, suggesting that differences in the ability to arouse from sleep may be related to the frequency and severity of nocturnal hypoxia.

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Introduction

Impairment of cerebral function can be induced by chronic hypoxia both experimentally and clinically (1, 2). Recurrent transient hypoxemia has been shown to be particularly frequent and profound during sleep in patients with chronic bronchitis and emphysema (3-5) but the frequency and duration of such nocturnal hypoxemic episodes vary considerably from patient to patient. We have previously shown that administration of oxygen improves cerebral function in chronic bronchitis and emphysema as assessed by the daytime electroencephalogram (EEG) (6). We have now studied a similar group of patients to see if their sleep is more disturbed than that of healthy subjects of similar age sleeping under the same conditions. We have also examined the relationship between the EEG pattern and the severity of nocturnal hypoxemia, and the effects on the EEG of improving oxygen saturation during the night by nocturnal oxygen therapy.

Methods

We studied 20 patients with chronic bronchitis and emphysema, 13 of whom were participants in the Medical Research Council's trial of domiciliary oxygen therapy (7). These 13 were of the "blue and bloated" type (7 men, 6 women); the remaining 7 were of the "pink and puffing" type (6 men, woman). All the patients had severe irreversible airflow obstruction. The "blue and bloated" patients showed significant daytime hypoxemia and hypercapnia, whereas the "pink and puffing" patients were less hypoxemic and did not retain carbon dioxide (table 1). No patient had had an exacerbation of chronic bronchitis for 6 wk prior study, none was receiving hypnotics, sedatives, or stimulant drugs, and none was more than 20% above his or her desired weight. All were treated with $beta_2$-sympathomimetic agents given by aerosol. Our control group was comprised of 9 subjects men and 4 women), all of whom were free from respiratory disease and had normal spirometric tests and a normal waking ear oxygen saturation. These subjects were drawn from hospital staff and a group of healthy volunteers.

The subjects slept in a quiet darkened room for 2 consecutive nights, the first night serving to accustom them to the monitoring equipment, and data were not collected until the second night of study. The whole night's sleep was recorded on an 8-channel Galileo EEG apparatus with the usual electrophysiologic technique including EEG (from 2 midline frontoparietal electrodes), electro-oculogram (from 4 frontal electrodes outside and above the outer canthi), and electromyogram (from 2 submental electrodes). Ear oxygen saturation was continuously recorded using a Hewlett-Packard 47201A ear oximeter, airflow at the mouth and nostrils was monitored by thermocouples mounted on nasal prongs, and anteroposterior thoracic movements were measured using an induction stethogram. These respiratory variables were recorded on paper and analyzed off-line. We considered arterial oxygen saturation (Sa_{O_2}) to be stable when it did not vary by more than 5% over a 15-min period and transient nocturnal hypoxemia to occur when the Sa_{O_2} fell from its previously stable level by more than 10% for longer than 1 min.

A computer-generated signal was recorded on the EEG trace every 15 min to provide a frame of synchronization for the oxygen saturation, respiration, and EEG sleep data. The sleep pattern was scored visually according to the standard criteria (8), except for the amplitude criteria of the slow wave Stages 3 and 4, which were decreased to 50 microvolts. The maximal amplitude of the slow waves of Stages 3 and 4 was also measured. All the EEGs were scored without knowledge of the type of subjects studied or the severity of nocturnal hypoxemia during that study.

Six of the "blue and bloated" patients (2 men and 4 women with a mean age of 60 ±

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TABLE 1

CLINICAL DETAILS OF 20 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND 9 NORMAL CONTROL SUBJECTS*

	"Blue bloated" (n = 13)	"Pink puffing" (n = 7)	Normal Subjects
Age, yr	57.4 ± 5.0	62.1 ± 7.0	53.0 ± 9.0
FEV_1, L	0.58 ± 0.18	0.75 ± 0.20	2.70 ± 1.0†
FVC, L	1.76 ± 0.67	1.95 ± 0.64	3.31 ± 1.1†
Ear oxygen saturation awake, %	80.0 ± 9.2†	94.1 ± 1.6†	97 ± 1.0†
Pa_{O_2}, mmHg	47.0 ± 6.8†	72.3 ± 4.8	—
Pa_{CO_2}, mmHg	51.4 ± 6.7†	36.0 ± 5.6	—

Definition of abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension.
* Values are expressed as mean ± SD.
† Significantly different ($p < 0.001$) from results in the other patients.

4 yr) who did not differ significantly from the rest of the "blue and bloated" group in the severity of their hypoxemia or airway obstruction (mean FEV_1, 0.6 ± 0.2 L; mean FVC, 1.5 ± 0.5 L; mean Pa_{O_2}, 48 ± 7 mmHg; mean Pa_{CO_2}, 50 ± 6 mmHg) were studied on 3 nights using similar techniques. On one of the nights after adaptation they breathed 2 L of air, whereas on the other 2 nights they breathed 2 L of oxygen given through nasal prongs on both occasions. The order of the air or oxygen nights was randomized and the subjects did not know which gas mixture they were receiving. All patients gave informed consent to the studies, which were approved by the Hospital Ethical Committee.

Statistical analysis was made using nonparametric tests, differences between subjects being compared with the Mann-Whitney U test and differences within subjects using Wilcoxon's signed rank test, as previously described (9). The degree of significance is given as for the two-tailed *t* test and all values are expressed as mean ± SD throughout.

Results

Comparison of the 2 patients groups and control subjects. The characteristics of nocturnal oxygenation in the 2 groups of patients with chronic obstructive airway disease and in the groups of normal subjects are summarized in table 2. Both groups of patients differed significantly from the normal control subjects in that they had a lower stable level of oxygen saturation during sleep, a greater number of transient hypoxemic episodes, and a greater fall in Sa_{O_2} during these episodes (all differences significant at $p < 0.002$). When the 2 groups of patients were compared with each other the "blue and bloated" patients showed a significantly lower stable Sa_{O_2} during sleep, more hypoxemic episodes, and a more profound fall in Sa_{O_2} during the hypoxemic episodes, than did the "pink and puffing" patients (all differences significant at $p < 0.01$). Transient hypoxemic episodes occurred predominantly during periods of hypoventilation and there was no significant difference in the incidence of hypoventilation in the 3 groups. No subject showed evidence of a sleep apnea syndrome when breathing air.

The sleep EEG. The time from the onset of sleep to the final awakening (total sleep period), the percentage of this time the subjects spent in the various sleep stages or awake, the amount of sleep proper (summed amount of Stages 2, 3, and 4 and REM), and some derived variables are shown in table 3.

The sleeping EEG of the patients compared with that of the normal control subjects was more disturbed, with a tendency to a longer sleep onset latency, more intervening wakefulness and drowsiness, less Stage 3 and 4 sleep, and less REM sleep. These differences, however, did not reach statistical significance because of the wide

TABLE 2

OXYGEN SATURATION DURING SLEEP IN 20 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND 9 NORMAL CONTROL SUBJECTS*

	BB (n = 13)	PP (n = 7)	Normal Subjects	Significance of Differences Between BB/N	PP/N	BB/PP
Stable Sa_{O_2} asleep, %	71 ± 14	92 ± 2	96 ± 1	$p < 0.002$	$p < 0.002$	$p < 0.002$
Lowest Sa_{O_2} asleep, %	39 ± 22	78 ± 14	86 ± 8	$p < 0.002$	ns‡	$p < 0.002$
Hypoxemic episodes† per night						
Total	3.3 ± 2.0	0.9 ± 1.1	0.3 ± 0.7	$p < 0.005$	ns	$p < 0.01$
In non-REM sleep	0.6 ± 1.0	0	0			
In REM sleep	2.7 ± 1.9	0.9 ± 1.1	0.3 ± 0.7			
Total duration of hypoxemic episodes per night, min	79 ± 58	13 ± 18	6 ± 15	$p < 0.01$		

Definition of abbreviations: BB = "blue and bloated" patients; PP = "pink and puffing" patients; Sa_{O_2} = arterial oxygen saturation measured by ear oximeter.
* Values are expressed as mean ± SD.
† A fall in Sa_{O_2} greater than 10% lasting longer than 1 min.
‡ Insufficient data points for comparison.

TABLE 3

SLEEP PATTERN IN 20 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND 9 NORMAL CONTROL SUBJECTS*

	BB (n = 13)	PP (n = 7)	Normal Subjects	Significance of Differences Between BB/N	PP/N	BB/PP
Sleep onset latency, min	35 ± 44	62 ± 46	20 ± 16	ns	$p < 0.02$	$p < 0.02$
Total sleep period, min†	361 ± 66	343 ± 94	399 ± 43	ns	ns	ns
Sleep proper, min‡	265 ± 89	219 ± 106	307 ± 54	ns	$p < 0.05$	ns
Total sleep period, %						
awake (stage 0)	17 ± 16	25 ± 19	14 ± 7			
stage 1	10 ± 4	12 ± 2	9 ± 5			
stage 2	51 ± 15	40 ± 11	49 ± 5	ns	ns	ns
stage 3	7 ± 5	6 ± 3	7 ± 2			
stage 4	4 ± 5	2 ± 3	5 ± 4			
stage REM	11 ± 7	15 ± 7	16 ± 6			
Mean duration of uninterrupted sleep episodes, min	6 ± 3	5 ± 2	10 ± 4	$p < 0.02$	$p < 0.05$	ns

For definition of abbreviations, *see* table 2.
* Values are mean ± SD.
† Time from sleep onset to final awakening.
‡ Summed duration of Stages 2, 3, 4, and REM sleep.

intersubject variability. Both groups of patients differed significantly ($p < 0.05$) from the control subjects in showing shorter duration periods of sleep between the brief episodes of arousal occurring during the night. The group of "blue and bloated" patients had less REM sleep than the normal subjects, whereas the "pink and puffing" patients showed a significantly longer sleep onset latency ($p < 0.02$) and a shorter duration of sleep proper ($p < 0.05$) than the healthy control subjects.

Comparison between the level of oxygenation and the characteristics of sleep. The transient falls in Sa_{O_2} were commoner during periods of REM sleep than during non-REM sleep in all groups of subjects (table 2). In the "blue and bloated" group the number of hypoxemic episodes per night occurring during REM sleep averaged 2.7 ± 1.9 compared with 0.6 ± 1.0 hypoxemic episodes occurring during non-REM sleep. The number of hypoxemic episodes was significantly higher in the "blue and bloated" patients with a greater amount of Stages 3 and 4 sleep ($p < 0.05$), and a nonspecific trend in the same direction was also seen in the "pink and puffing" group ($0.05 < p < 0.1$). In the "pink and puffing" patients the hypoxemic episodes were more frequent in those with a greater amount of REM sleep ($p < 0.05$); this relationship was not significant in the "blue and bloated" group. In both groups of patients the number of hypoxemic episodes was greater in those subjects showing less intervening wakefulness and drowsiness and this relationship was significant at 2% in both groups combined (figure 1).

The duration of hypoxemic episodes was not significantly related to any of the sleep characteristics examined. However, the stable level of oxygen saturation during sleep was positively correlated with the amount of REM sleep; patients with the lowest stable level of nocturnal oxygen saturation had the fewest periods of REM sleep ($p < 0.05$).

The effect of correcting nocturnal hypoxemia. The 6 hypoxic "blue and bloated" patients studied breathing air or oxygen at 2 L/min via nasal prongs showed a similar sleep disturbance to the group as a whole when breathing air, the only significant difference was longer sleep onset latency in this subgroup (table 4). During the night's sleep

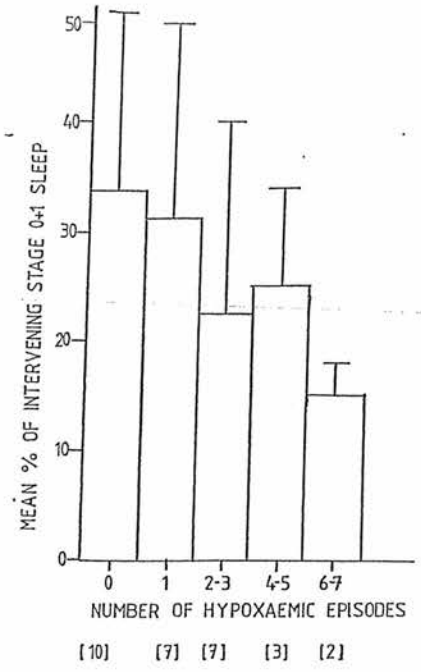

Fig. 1. Relationship between sleep disturbance and number of hypoxemic episodes. The greater number of hypoxemic episodes, the less disturbed the patient's sleep. Figures in parentheses refer to number of subjects with that frequency of hypoxemic episodes. Results given as mean ± SD.

breathing air, an average of 3.7 hypoxemic episodes were observed with a mean duration of 31 min, the lowest Sa_{O_2} reached varying from 74 to 10%. When breathing oxygen all patients showed an improvement in their level of nocturnal oxygen saturation and sleep pattern. The mean number of hypoxemic episodes was reduced and their duration consistently decreased from 31 to 20 min. In 2 patients no hypoxemic episodes occurred during the oxygen treatment night.

Sleep onset latency fell during the night breathing oxygen, whereas the amount of sleep proper (Stages 2, 3, 4, and REM) increased in 5 of the 6 patients ($0.05 < p < 0.1$). The amount of intervening wakefulness and drowsiness decreased ($p < 0.05$) in all 6 patients and averaged 15% of the total sleep. The number of periods of REM sleep increased significantly as did the amount of REM sleep. The duration of Stages 3 and 4 reached an unusually high level of 20% but this change was not significant because of the wide variability within the subjects. The mean duration of uninterrupted episodes of sleep (Stages 2, 3, 4, and REM) increased in 5 of the 6 patients from a group mean of 6.7 to 10.3 min while breathing oxygen. The majority of the hypoxemic episodes occurred during the period of REM sleep whether breathing air or oxygen.

Discussion

Severe airway obstruction is known to be associated with frequent and profound episodes of nocturnal oxygen desaturation especially if the patient is already hypoxic during the day (4, 5). These episodes of additional hypoxemia are usually associated with periods of relative hypoventilation (10), as was the case in these studies, and can increase the resting pulmonary artery pressure (5).

Significant disturbances in the sleeping EEG have been reported in patients with a similar degree of airway ob-

TABLE 4

THE EFFECTS OF IMPROVING OXYGENATION ON SLEEP IN 6 SUBJECTS WITH HYPOXIC CHRONIC BRONCHITIS AND EMPHYSEMA*

	Breathing Air	Breathing Oxygen	
Stable Sa_{O_2} awake, %	81 ± 6	97 ± 2	($p < 0.05$)
Mean stable Sa_{O_2} asleep, %	53 ± 23	90 ± 9	($p < 0.05$)
Lowest Sa_{O_2} asleep, %	33 ± 27	76 ± 17	($p < 0.05$)
Hypoxemic episodes† per night, n	3.7 ± 2.2	1.5 ± 1.6	($p < 0.05$)
Sleep onset latency, min	52 ± 60	20 ± 13	($0.05 < p < 0.1$)
Total sleep period, min‡	336 ± 60	395 ± 40	ns
Sleep proper, mins§	247 ± 82	334 ± 29	($0.05 < p < 0.1$)
Total sleep period, %			
Stage 0 + 1	27 ± 18	15 ± 8	($p < 0.05$)
Stage 2	51 ± 17	49 ± 14	ns
Stage 3 + 4	11 ± 9	20 ± 11	ns
Stage REM	11 ± 7	17 ± 6	($p < 0.05$)
Duration of uninterrupted sleep, min	6.8 ± 3.4	10.3 ± 3.9	($0.05 < p < 0.1$)
REM periods, n	2.7 ± 1.0	4.2 ± 1.0	($p < 0.05$)

For definition of abbreviations, *see* table 2.
* Values are expressed as mean ± SD.
† A fall in Sa_{O_2} greater than 10% lasting longer than 1 min.
‡ Time from sleep onset to final awakening.
§ Summed duration of Stages 2, 3, 4, and REM sleep.

struction, the sleep period time and amount of sleep proper (summed Stages 2, 3, 4, and REM) being reduced when compared with control subjects of similar age (4). However, in the above studies the patients slept for only one night study in unfamiliar surroundings, wearing a variable amount of monitoring equipment. Furthermore, the results of these single night studies have been compared with retrospective studies carried out with better acclimatization and without the same amount of monitoring apparatus. The disturbance in sleep pattern that we now report still had a nonspecific component to incomplete adaptation, as shown by the lower percentage of REM sleep in our control group (16%), when contrasted with a normal value of approximately 22% for similar age groups (11, 12). Nevertheless, the total sleep duration for our more severely disabled "blue and bloated" patients was 361 ± 66 min, considerably longer than the 266 ± 136 min in the one night study of similar patients reported by Wynne and colleagues (4). Because we were interested in the amount of disturbed sleep shown by our groups of patients and control subjects we concentrated on the total sleep period rather than on the total sleep time in our analysis because the latter term excludes the stages awake during the night's sleep.

Although the total duration of sleep was not significantly reduced when compared with that of similarly aged and acclimatized normal control subjects, there was evidence of more sleep disturbance in the patients with airway obstruction. They took longer to fall asleep, had more intervening wakefulness, and less Stages 3 and 4 and REM sleep. However, other differences between the groups emerged that could not be attributed to the irreversible airway obstruction that was of similar severity in both "blue and bloated" and "pink and puffing" patients. Although the "blue and bloated" had a significantly greater fall in Sa_{O_2} than the "pink and puffing" patients, to our surprise it was the "pink and puffing" patients who had the most disturbed sleep as shown by the EEG recordings. Similarly, even within any group, the patients with more frequent episodes of hypoxemia had EEG characteristics usually associated with "good sleep," e.g., less intervening wakefulness and drowsiness, and more Stages 3 and 4 sleep. These results are supported by the findings of Demarco and coworkers (13) who studied 6 "pink and puffing" and 4 "blue and bloated" patients for one night only. The "pink and puffing" patients spent 43.4% of the total sleep period in Stages 0 and 1 sleep compared with 36.7% in the 4 "blue and bloated" patients who also spent more of the night in Stages 3 and 4 sleep. These results suggest that the disturbance of sleep might have a protective effect in preventing the development of profound hypoxemia.

The 6 "blue and bloated" patients who were studied without and during nocturnal oxygen administration had fewer episodes of transient nocturnal hypoxemia when breathing oxygen, probably reflecting their different starting point on the oxygen dissociation curve (10). When breathing oxygen there was a significant reduction in the amount of Stages 0 and 1 sleep, and an increase in REM sleep. The total sleep period and the distribution of sleep stages in this group of "blue and bloated" patients when breathing oxygen resembles that seen in the control subjects rather than that seen in the normally better oxygenated "pink and puffing" patients with an equivalent degree of airflow obstruction. This objective evidence of more normal sleep supports the frequent subjective observations made by patients who start nocturnal oxygen therapy that they get a better night's sleep as a result of this treatment and waken less frequently. It may also account for the improved neuropsychologic function observed in patients receiving long-term domiciliary oxygen therapy (14).

It has been suggested that the variation in the ventilatory response to hypoxia and hypercapnia may account for the variation in prevalence of arousal from sleep in humans (15). Patients with hypoxic chronic bronchitis and emphysema have a reduced hypoxic drive to breathing when studied awake (16), and it is possible that this reduction in the ventilatory response to hypoxia contributes to the relatively "good" sleep quality of these patients. Animal studies suggest that a reduced CO_2 response occurs during REM sleep (17) but the significance of this in humans is not clear because only small changes in the directly measured arterial CO_2 tension are seen during the hypoxemic episode (10). Animal experiments also suggest that the hypoxic drive is preserved during REM sleep but recent measurements in normal human subjects have found it to be diminished (18). It is possible that some of the differences in the clinical course of patients with chronic obstructive airway disease may depend upon the interplay of factors such as the hypoxic and hypercapnic ventilatory drives and the sleep arousal threshold, which determine whether sleep is disturbed, while the arterial Po_2 is maintained relatively normal as in the "pink and puffing" patients or whether the quality of sleep is good but profound hypoxia develops as in the "blue and bloated" patients.

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Cigarette Smoking and Secondary Polycythemia in Hypoxic Cor Pulmonale[1,2]

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SUMMARY We have related the red cell mass (RCM) in 47 hypoxic patients with COPD (mean P_{O_2}, 52.5 ± 5.2 SD mmHg; mean P_{CO_2}, 51.7 ± 6.7 mmHg; mean FEV_1, 0.6 ± 0.2 L; mean FVC, 1.7 ± 0.6 L) to their smoking habits and outpatient carboxyhemoglobin concentrations. The mean RCM was 42.5 ± 8.0 ml/kg in the 31 patients who still smoked, significantly ($p < 0.01$) higher than in the 16 who were currently nonsmokers (RCM, 29.7 ± 4.4 ml/kg). Measurements of arterial P_{O_2}, pH, P_{50}, and COHb showed that the saturation of available hemoglobin ($S_{O_2}A$) was less well correlated ($r = -0.36$, $p < 0.05$) with RCM in the smokers, than was $S_{O_2}T$ ($r = -0.58$, $p < 0.001$), $S_{O_2}T$ including a corrective term for COHb. The RCM correlated well with the mean outpatient COHb measured repeatedly over 6 to 36 months in 40 of the patients but poorly with their average arterial oxygen saturation ($r = 0.15$, $p > 0.1$). In 15 patients given long-term oxygen therapy (15 hours/24-hour period) for 12 months RCM decreased significantly only in those who stopped smoking, as shown by a decrease in COHb. We conclude that cigarette smoking may determine the severity of secondary polycythemia in patients with hypoxic COPD, and prevent its correction by long-term oxygen therapy.

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Introduction

Secondary polycythemia is well recognized as a physiologic response to the reduced arterial oxygen saturation (Sa_{O_2}) occurring at high altitude (1). However, the degree of polycythemia at any degree of Sa_{O_2}, as shown by red cell mass (RCM) is much more variable in patients who are hypoxic as a result of chronic bronchitis and emphysema (2-4). Secondary polycythemia has also been described in heavy smokers who had normal respiratory function, and has been attributed to the raised carboxyhemoglobin concentrations resulting from their inhalation of carbon monoxide (CO) in cigarette smoke. Furthermore, this secondary polycythemia is partially corrected when these patients stopped smoking, thus restoring their circulating carboxyhemoglobin concentrations to normal (5).

We measured the carboxyhemoglobin concentration, arterial oxygen saturation, and RCM in patients with severe chronic bronchitis and emphysema in an attempt to explain the variability in the extent of their secondary polycythemia. We also studied the effects of correcting arterial hypoxemia by long-term oxygen therapy, given for 15 hours in a 24-hour period, on the polycythemic response in 15 of these patients, 7 of whom continued to smoke during the time when they were not receiving oxygen, despite repeated advice to stop.

Methods

Forty-seven patients with hypoxic cor pulmonale secondary to chronic bronchitis and emphysema were initially assessed when clinically stable, as judged by constant body weight, FEV_1, and measurements of arterial blood gas tensions over 4 wk (table 1). All were then free from respiratory infection and pulmonary edema, but had arterial hypoxemia (mean P_{O_2}, 52.5 ± 5.2 SD mmHg) when breathing air, and severe irreversible airway obstruction (FEV_1, 0.6 ± 0.2 L). None had splenomegaly, a raised platelet count, or a raised leukocyte count to suggest that their polycythemia might be primary. Red cell mass and plasma volume were measured simultaneously by intravenously administered autologous [^{51}CR]erythrocytes and [^{131}I]albumin (6). Arterial carboxyhemoglobin concentrations (COHb) were measured initially, and then at two monthly intervals, with an IL182 Co-oximeter (7). The patients were classified as either smokers or nonsmokers on the basis of their smoking history, and patients were accepted as nonsmokers only if their current COHb was less than 3%, and they also stated that they had not smoked cigarettes for the preceding 2 yr.

The oxygen tension at 50% hemoglobin saturation (P_{50}) was measured by tonometering blood with three different gas mixtures, all of which had a P_{CO_2} of 40 mmHg, but the P_{O_2} was adjusted to give oxygen saturations (S_{O_2}) of 40, 50, and 60%. The P_{50} at pH 7.4 and zero base excess was then obtained by interpolation on Hill's logarithmic plot of the oxygen dissociation curve (ODC). Arterial oxygen saturation may be expressed as the saturation of the total oxygen binding sites ($Sa_{O_2}T$):

$$Sa_{O_2}T = \frac{Hb_{O_2}}{Hb_{O_2} + Hb + Hb_{CO}} \times 100,$$

which includes the binding sites occupied by CO, Hb_{O_2} being the concentration of oxygenated hemoglobin, Hb being the concentration of reduced hemoglobin, and Hb_{CO} being the concentration of hemoglobin combined with carbon monoxide. An alternative is to express saturation in terms of those sites that are available for oxygen binding (8), this term being $Sa_{O_2}A$:

$$Sa_{O_2}A = \frac{Hb_{O_2}}{Hb_{O_2} + Hb} \times 100.$$

The $Sa_{O_2}A$ therefore ignores any hemoglobin that is combined with CO, and is the expression used in figure 1. We have also calculated $Sa_{O_2}A$ and $Sa_{O_2}T$ in 40 patients, using the measured arterial P_{O_2} when breathing air, the directly measured P_{50}, and the average of that patient's carboxyhemoglobin values, as measured at afternoon outpatient clinics, every two months, over 4 to 36 months.

Red cell mass and plasma volume estimations were repeated in 15 patients who received long-term oxygen therapy for 15 h in a 24-h period, over a period of at least 12 months (9, 10). Treatment compliance was assessed by unannounced home visits and monitoring reservoir weight in those patients on liquid oxygen systems, and

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TABLE 1

RESPIRATORY FUNCTION, OXYGEN SATURATION, RED CELL MASS, AND PLASMA VOLUME IN 47 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

Group	Number	FEV_1 (*l*)	FVC (*l*)	Po_2 (*mmHg*)	Pco_2 (*mmHg*)	pH	$Sa_{O_2}A$	$Sa_{O_2}T$	RCM (*ml/kg*)	PV (*ml*)	P_{50} (*mmHg*)
All patients	47	0.6 ± 0.2	1.7 ± 0.6	52.5 ± 5.2	51.7 ± 6.7	7.38 ± 0.04	86 ± 4.0	82 ± 5.5	37.6 ± 9.3	39.0 ± 6.0	25.4 ± 2.35
All smokers	31	0.6 ± 0.2	1.8 ± 0.6	52.5 ± 5.2	53.2 ± 6.0	7.38 ± 0.04	86 ± 4.0	80 ± 5.4	42.5 ± 8.0	41.5 ± 6.0	24.4 ± 1.8
All nonsmokers	16	0.56 ± 0.2	1.6 ± 0.5	53.5 ± 4.5	49.5 ± 7.5	7.39 ± 0.03	86 ± 3.7	85 ± 4.0	29.7 ± 4.4	35.5 ± 3.5	27.4 ± 1.9
All men	27	0.7 ± 0.2	1.9 ± 0.6	53.5 ± 5.2	51.0 ± 6.7	7.39 ± 0.04	86 ± 4.7	82 ± 6.0	40.0 ± 9.0	40.0 ± 6.0	25.1 ± 2.4
All women	20	0.6 ± 0.2	1.3 ± 0.3	51.7 ± 4.5	53.5 ± 6.7	7.38 ± 0.03	85 ± 3.5	82 ± 4.8	34.5 ± 9.4	39.0 ± 6.0	26.0 ± 2.2

Definition of abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; Po_2 and Pco_2 = arterial oxygen and arterial carbon dioxide tensions, respectively; RCM = red cell mass; PV = plasma volume; P_{50} = oxygen tension at 50% saturation.

cylinder usage in the other patients. Repeated COHb measurements showed that 7 of these patients continued to smoke, for the period in the day when they were not taking oxygen despite our repeated advice to stop, whereas the remaining 8 patients stopped smoking during the 12 months of long-term oxygen treatment.

The significance of difference of mean values was determined by the unpaired *t* test, multiple regression relationships, and correlations being made by the least squares method. The measurements of RCM before and after long-term oxygen therapy was compared by Wilcoxon's rank sum test, as the normality of these distributions could not be assumed. Values are given as mean ± 1 SD.

Results

There was no significant difference in age, severity of airway obstruction, resting Po_2, Pco_2, pH, or $Sa_{O_2}A$ between the 31 patients who smoked and the 16 nonsmokers ($p > 0.1$, table 1).

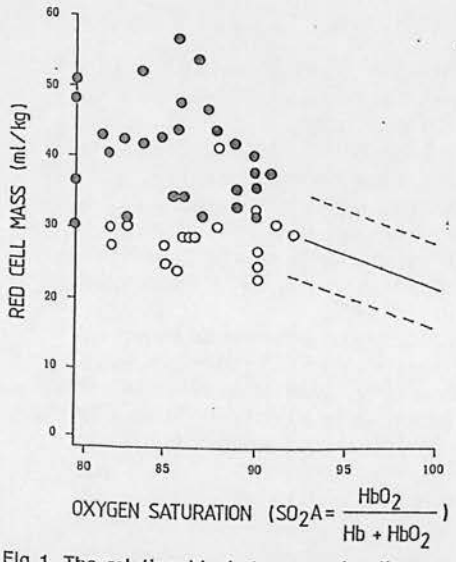

Fig. 1. The relationship between red cell mass and oxygen saturation in 47 patients with chronic bronchitis and emphysema. Confidence limits derived from normal data of Weil and coworkers (1). Solid circles = smokers; open circles = current nonsmokers.

However, in the 31 smokers the RCM (mean 42.5 ± 8.0 ml/kg) was significantly higher ($p < 0.01$) than in the 16 nonsmokers (mean RCM, 29.7 ± 4.4 ml/kg) (figure 1), and the plasma volume in the smokers (41.5 ± 6.2 ml/kg) was significantly higher ($p < 0.01$) than in the nonsmokers (35.3 ± 3.5 ml/kg). As a result, the difference in packed cell volume between smokers and nonsmokers was less pronounced than that seen in RCM measurements.

The relation between the RCM and $Sa_{O_2}A$ was different in the smokers from what it was in the nonsmokers, the smokers tending to have a higher value of RCM for any reduction in $Sa_{O_2}A$ (figure 1). However, the correlation between RCM and $Sa_{O_2}A$ was weak in both smokers ($r = -0.36$, $p < 0.05$) and nonsmokers ($r = -0.24$, $p < 0.1$). In contrast, the correlation between RCM and $Sa_{O_2}T$ was more significant in the 31 smokers ($r = -0.58$, $p < 0.01$) but there was no significant correlation between RCM and either $Sa_{O_2}A$ or $Sa_{O_2}T$ in the 16 nonsmokers.

In 40 patients (24 men, 16 women), repeated measurements of Pa_{O_2} and COHb were made at an afternoon outpatient clinic over 6 to 36 months of follow-up. Between 4 and 16 measurements of COHb were made in each patient; these varied only by 1 to 2% in any individual patient. There was a significant relation between the average of the COHb values in each patient, and that patient's RCM ($r = 0.73$, $p < 0.01$) (figure 2). Once the carboxyhemoglobin concentration was taken into account, the addition of $Sa_{O_2}A$ to a multiple regression analysis of this data did not add significantly to the prediction of RCM.

The RCM was higher in men (40.0 ± 9.0 ml/kg) than in women (34.5 ± 9.4 ml/kg), but as more of the men were smokers, this may have accounted for some of this difference. There was no significant relation between the plasma volume and either $Sa_{O_2}A$ or $Sa_{O_2}T$, in either smokers or nonsmokers, and there was no difference in plasma volume measurements between men and women.

The physiologic variables recorded in 15 patients who were restudied are shown in table 2. There was no significant difference in the severity of hypoxemia, CO_2 retention, pulmonary hypertension, or polycythemia in either group at the time of initial assessment, and treatment compliance was good in both the smoking and nonsmoking patients. Despite receiving 12 months of long-term oxygen therapy (given for 15 h in a 24-hour period), there was no significant change in RCM in the 7 patients who continued to smoke, in whom the COHb values remained high (figure 3). In contrast, in the 8 patients who stopped smoking, as confirmed by a decrease in COHb to 1.8 ± 0.4%, RCM decreased from a mean value of 43.4 ml/kg to 28.0 ml/kg during the year when they were given long-term oxygen therapy. This difference was very significant ($p < 0.001$). Likewise, packed cell volume and mean pulmonary artery pressure only decreased significantly in those patients who stopped smoking.

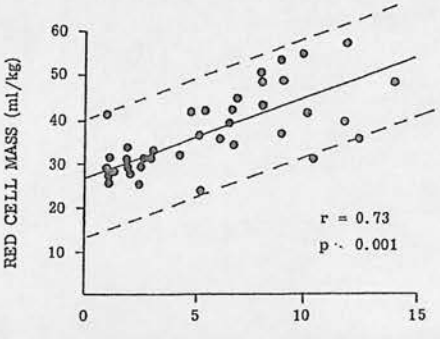

Fig. 2. The relationship between red cell mass and mean outpatient carboxyhemoglobin concentration in 40 patients with chronic bronchitis and emphysema.

TABLE 2*

PHYSIOLOGIC MEASUREMENTS IN SMOKING AND NONSMOKING PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA BEFORE AND AFTER 12 MONTHS OF DOMICILIARY OXYGEN THERAPY

	Still Smoking		Stopped Smoking	
	Initial (n = 7)	1 Year (n = 7)	Initial (n = 8)	1 Year (n = 8)
FEV_1, L	0.66 ± 0.15	0.61 ± 0.1	0.53 ± 0.14	0.53 ± 0.13
FVC, L	1.69 ± 0.4	1.48 ± 0.4	1.56 ± 0.6	1.49 ± 0.57
Pa_{O_2}, mmHg	54.7 ± 4.0	51.5 ± 5.8	52.0 ± 4.0	48.6 ± 5.8
Pa_{CO_2}, mmHg	53.0 ± 4.0	53.0 ± 4.4	53.6 ± 1.5	56.0 ± 6.8
PCV, %	54.0 ± 4.7	51.0 ± 7.4	53.0 ± 3.8	43.6 ± 2.8
PAP, mmHg	30.6 ± 4.5	29.4 ± 9.4	38.7 ± 7.4	25.0 ± 4.6*
RCM, ml/kg	40.9 ± 8.0	39.1 ± 10.4	43.4 ± 7.4	28.0 ± 5.4†
COHb, %	8.34 ± 3.0	10.0 ± 3.0	6.8 ± 1.3	1.8 ± 0.4†

Definition of abbreviations: PCV = packed cell volume; PAP = mean pulmonary artery pressure; COHb = carboxyhemoglobin concentration. For other abbreviations, *see* table 1.

* Initial and 1-year values differ significantly ($p < 0.01$).

† Initial and 1-year values differ significantly ($p < 0.01$).

Discussion

The decrease in arterial oxygenation in healthy residents at high altitude is accompanied by a fairly predictable increase in RCM(1). Whereas the relation between Pa_{O_2} and RCM was curvilinear in that study, the relation between $Sa_{O_2}A$ and RCM was linear (1). We have therefore calculated correlations between $Sa_{O_2}A$ (or $Sa_{O_2}T$) and RCM in this study, and not between RCM and Pa_{O_2}. As noted previously (2, 11) the variability of this relationship in patients with hypoxemia caused by chronic bronchitis and emphysema was considerably greater than that seen in healthy subjects (figure 1) although the degree of airway obstruction, arterial hypoxemia, and CO_2 retention among our patients was relatively similar (table 1) when they were breathing air at rest. It therefore appears reasonable to search for some other factor than arterial hypoxemia to account for this greater variation in polycythemic response.

Inhaled cigarette smoke contains carbon monoxide produced by incomplete combustion of tobacco. In our experience, carboxyhemoglobin concentrations commonly lie between 5 and 15% in our patients who continue to smoke, when measured at an afternoon outpatient clinic. We thus sought to explain the excessive polycythemic response in our smoking patients by relating RCM to average COHb concentrations in each patient, using the average COHb values measured at these afternoon clinics during several months. The positive correlation observed (figure 2) suggests that the increased COHb concentrations in the smokers could indeed contribute to their polycythemic response, and this was supported by the multiple regression relationships between RCM, $Sa_{O_2}A$, and COHb, which implies that carboxyhemoglobin was more important than the degree of arterial oxygenation in terms of effect on the RCM.

The greater polycythemic response in our smokers may therefore arise from impairment in delivery of oxygen to the site of release of erythrogenin in their kidneys (11) as a result of these high concentrations of circulating carboxyhemoglobin. Carbon monoxide not only binds to sites on the hemoglobin molecule, which would otherwise bind oxygen (thus diluting the amount of available hemoglobin), but such binding also affects the affinity of the remaining binding sites for oxygen, thus changing the position (P_{50}) of the oxygen dissociation curve (8). We calculated oxygen saturations from measured values of Pa_{O_2}, and pH, using the P_{50} actually measured in each patient at the time that the RCM was determined. We thereby calculated the relationship between RCM and the arterial oxygen saturation, expressed as either $Sa_{O_2}T$ (including the mean COHb) or as $Sa_{O_2}A$ (which ignores the COHb concentration). The correlation between $Sa_{O_2}A$ and the RCM was only significant at 5% in the smokers, but this correlation became significant at 1% when $Sa_{O_2}T$ was substituted for $Sa_{O_2}A$. Furthermore, the relationship between either $Sa_{O_2}A$ or $Sa_{O_2}T$ was insignificant in the nonsmokers who had very low concentrations of COHb, despite similar degrees of arterial hypoxemia to that found in the smokers (table 1). Many of the nonsmokers had values of RCM that lay within our normal range, but of course also had COHb concentrations that were normal. These results would thus support the proposal that the prevailing degree of circulating carboxyhemoglobin is an important determinant of the polycythemic response.

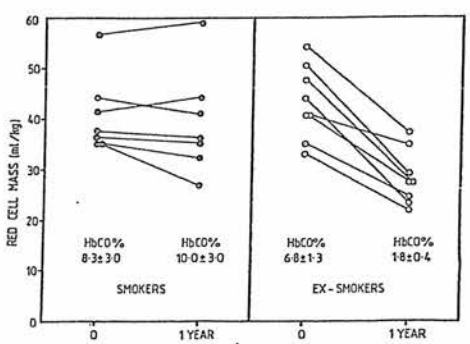

Fig. 3. The effect of smoking on red cell mass in 15 patients with COPD treated with domiciliary oxygen for 12 months.

This notion receives further support from our studies on patients receiving long-term domiciliary oxygen therapy. When this treatment was used to raise the average arterial P_{O_2} over 60 mmHg, the hypoxic stimulus to polycythemia would thus be reduced, as occurs when high altitude residents return to sea level. Nevertheless, in seven of our patients who were treated with oxygen but who nonetheless continued to smoke during the 9 h of the 24-h period when they were not receiving oxygen therapy, the RCM did not decrease significantly over the course of the year of oxygen treatment. In contrast, in the eight patients who did discontinue smoking, as shown by a decrease in COHb concentrations, this long-term oxygen therapy was then associated with a significant reduction in RCM ($p < 0.001$) (figure 2). Similar failures to reduce packed cell volume by long-term oxygen therapy in cigarette smokers have been noted previously (12). Thus, carbon monoxide inhaled in cigarette smoke appears to enhance the polycythemic response to hypoxia in patients with hypoxic chronic bronchitis and emphysema, but a significant account of the variability in the RCM still remains unexplained. Exercise often increases the severity of hypoxemia in these patients (13). Furthermore, transient episodes of severe nocturnal hypoxemia have recently been observed in similar patients with the 'blue and bloated' (Type B, nonfighter)

pattern of chronic bronchitis and emphysema (14), and some of the patients in whom these observations were made were included in this present study. These significant variations in oxygen tension could well account for some of the remaining variability in the polycythemic response seen in our patients.

In practical terms, our study provided further evidence that stopping cigarette smoking can correct some of the pathophysiologic abnormalities, even in those patients who suffer from a very advanced stage of chronic bronchitis and emphysema. In addition, it implies that some of the physiologic benefit to be expected from long-term oxygen therapy will not be achieved if the patient continues to smoke at least some of the time while receiving this treatment. As a result of these observations, we will no longer recommend this expensive treatment for patients who have persistently high concentrations of carboxyhemoglobin despite repeated advice to stop smoking cigarettes.

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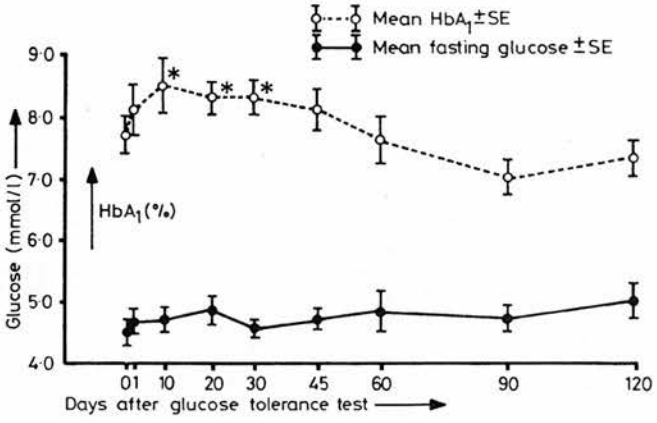

Glucose and HBA_1 values in the 120 days after an oral glucose tolerance test. *Result differs significantly from baseline value ($p<0.05$).

concentration of some 2·5 mmol/l could produce a significant increase in HbA_1 concentration of almost 1% of total haemoglobin and that this increase appeared 10 days after the hyperglycaemia and values remained high until 30 days later, then fell to normal by 60 days after the test. These data differ slightly from those of a similar study[2] in which 75 g glucose was used in that we observed a significant rise in HbA_1 concentration earlier.

These findings raise doubts about the validity of using HbA_1 concentrations as an index of time-integrated blood glucose concentration since the blood sugar concentrations of insulin-dependent diabetics may vary widely and frequently throughout the day. This criticism would not apply, of course, in uncontrolled or poorly controlled diabetics, in whom persistent significant increases in blood glucose concentrations produce a marked increase in HbA_1 values. In these circumstances there is no doubt about the value of HbA_1 measurement. Perhaps, however, HbA_1 measurements are too sensitive in well-controlled insulin-dependent diabetics and those with mild maturity onset diabetes since our findings show that a minor transient period of hyperglycaemia will result in a significant increase in HbA_1 concentrations.

It is now established that there is an unstable component of HbA_1 (Schiff base fraction) which accounts for the rapid increase in HbA_1 values in response to a short-term increase in blood glucose concentration.[3] The microcolumn technique does not differentiate between unstable and stable (ketoamine) fractions of HbA_1, but an increase in the unstable fraction would be expected to produce some increase in total HbA_1. We did not observe this during the glucose tolerance test or the next morning, but possibly the degree of hyperglycaemia might not have been sufficient to produce this effect. Alternatively we may have missed the effect occurring later in the day of the test. The labile fraction is thought to decrease again within six hours, once normoglycaemia is achieved,[4] so it may have disappeared by the following morning.

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Carbon monoxide and exercise tolerance in chronic bronchitis and emphysema

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Abstract

The effects of carbon monoxide on exercise tolerance as assessed by the distance walked in 12 minutes were studied in 15 patients with severe chronic bronchitis and emphysema (mean forced expiratory volume in one second 0·56 l, mean forced vital capacity 1·54 l). Each subject walked breathing air and oxygen before and after exposure to sufficient carbon monoxide to raise their venous carboxyhaemoglobin concentration by 9%. There was a significant reduction in the walking distance when the patients breathed air after exposure to carbon monoxide ($p<0.01$), and the significant increase in walking distance seen after exercise when breathing oxygen at 2 l/minute via nasal cannulae was abolished if carbon monoxide had previously been administered.

Thus concentrations of carboxyhaemoglobin frequently found in bronchitic patients who smoke may reduce their tolerance of everyday exercise, possibly by interfering with the transport of oxygen to exercising muscles.

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Introduction

British cigarettes produce appreciable quantities of carbon monoxide, which is formed by the incomplete combustion of tobacco in those cigarettes without ventilated filters. When inhaled this carbon monoxide readily combines with haemoglobin to form carboxyhaemoglobin. Carboxyhaemoglobin concentration has been related to cigarette consumption,[1] and concentrations of 5-15% are common in patients who continue to smoke (table I). In normal healthy volunteers the maximum oxygen uptake during bicycle exercise was reduced when the carboxyhaemoglobin concentration was raised to 20% by

inhalation of carbon monoxide, but this effect was seen only at the highest work loads.[2] Thus carbon monoxide inhaled from cigarettes might contribute directly to the reduced exercise tolerance of patients with chronic bronchitis and emphysema who continue to smoke. We measured the distance walked on the level within 12 minutes in 15 such patients to assess their exercise tolerance before and after they breathed a low concentration of carbon monoxide sufficient to raise their carboxyhaemoglobin concentration by 9%.

Patients and methods

We studied 15 outpatients (11 men and four women) with severe irreversible airways obstruction (mean (±SD) forced expiratory volume in one second (FEV_1) 0·56±0·2 l; mean forced vital capacity (FVC) 1·54±0·4 l) who were hypoxic and retaining carbon dioxide at rest (mean arterial pressure of oxygen 6·83±0·65 kPa (51·2±4·9 mm Hg), mean arterial pressure of carbon dioxide 6·33±0·7 kPa (47·5±5·3 mm Hg); mean arterial pH 7·39±0·02) (see table II). All patients were clinically stable at the time of study, and those who smoked were asked to stop smoking for 12 hours before each study. All studies were carried out in the afternoon, the FEV_1 and FVC being measured before and at the end of each study. The results in any patient who showed a change of more than 0·1 l in FEV_1 during the study period were discarded.

A venous cannula was inserted in the antecubital fossa and blood withdrawn for estimation of carboxyhaemoglobin concentration on attendance, during and after inhalation of 0·02% carbon monoxide from a Douglas bag, and immediately after the end of the final walk. Carboxyhaemoglobin concentration was measured with an IL 182 Co-oximeter.[3] In eight patients we also measured arterial oxygen saturation non-invasively using a Hewlett Packard HP47201A ear oximeter before and immediately after the end of the walk. These values were corrected for the carboxyhaemoglobin concentration.[4]

The patients walked at their own pace in a level corridor, the distance walked in 12 minutes (including stops if so desired) being recorded. All patients wore lightweight nasal prongs, giving either air or oxygen at a rate of 2 l/minute delivered from a cylinder that was pushed behind by a technician, who did not know what gas was being given. Six subjects also wore lightweight electrocardiographic chest leads, which permitted recording of the electrocardiogram at the end of the walk. In the other subjects the pulse rate was measured before and at the end of each walk.

Each subject attended on two afternoons and walked four times during each afternoon. After spirometry and blood sampling they walked when breathing 2 l air/minute, then sat at rest for 20 minutes, and then walked again breathing 2 l oxygen/minute. After another 20-minute rest they inhaled 0·02% carbon monoxide in air from a Douglas bag through a mouthpiece and noseclip for 20-30 minutes until their venous carboxyhaemoglobin concentration was 8-12% above the initial value measured when they arrived for the study. The two 12-minute walks were then repeated in the same order as before. At the next visit, seven to 14 days later, the order of breathing air and oxygen was reversed, both before and after inhaling carbon monoxide. The results for the two walks were then pooled to eliminate any training effect and to minimise errors due to fatigue. As carbon monoxide is eliminated from the blood with a half life of four hours[5] it was not possible to repeat the walks with the high carboxyhaemoglobin concentrations first.

The results were analysed by the Wilcoxon signed rank test as normality of distribution could not be assumed. Values were expressed as mean±SD or as a range.

Results

The initial venous carboxyhaemoglobin concentration when the patients were breathing air before exercise was 3·1% (range 1·1-5·4%), and this increased to 12·3% (range 9·6-14·9%) after inhalation of carbon monoxide. There was a tendency for the concentration to fall during the second period of exercise, so that the mean at the end of exercise was 10·8% (range 8·5-12·8%). This, however, was a constant effect and affected equally the walks when patients were breathing air and when they were breathing oxygen, as the order of walking was reversed at the end of the second visit. Although the values of FEV_1 and FVC were similar (table II), the distance walked when breathing air varied from 252 to 1075 m in the different patients and these distances were not significantly correlated with the FEV_1 or FVC.

When the distance walked by each patient was compared for the various gas mixtures (figure), breathing 2 l oxygen/minute increased the mean distance walked by 53·7 m ($p < 0·01$) over that walked when breathing air without a raised carboxyhaemoglobin concentration. Increasing the carboxyhaemoglobin concentration to 12·3±1·4% reduced the distance walked when breathing air by 42·7 m ($p < 0·01$). When patients had a raised carboxyhaemoglobin concentration and breathed oxygen the mean distance walked increased (as compared with that when breathing air with a raised carboxyhaemoglobin concentration) by 79·3 m ($p < 0·01$). The distance walked when

TABLE I—*Mean carboxyhaemoglobin concentrations in 91 patients with chronic bronchitis and emphysema attending afternoon outpatient clinic**

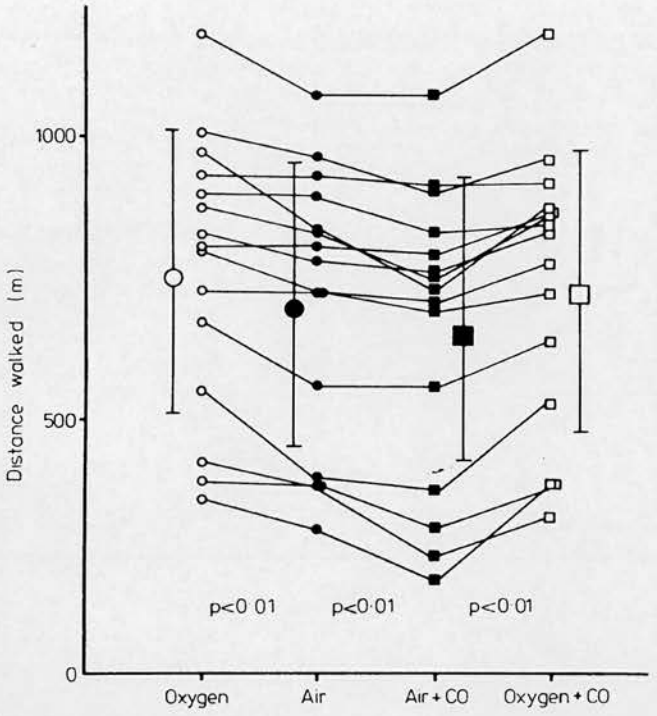
Carboxyhaemoglobin (%):	0–1	−2	−3	−4	−5	−6	−7	−8	−9	−10	−11	−12	−13	−14	−15
No of patients:	5	19	13	8	5	9	6	2	8	2	6	4	3		1

*Patients with concentrations up to 3% were probably non-smokers.

TABLE II—*Spirometric results, arterial blood gas tensions, changes in carboxyhaemoglobin concentrations from baseline values after inhalation of carbon monoxide (CO), and 12-minute walking distance in 15 patients with chronic bronchitis and emphysema*

Case No	FEV_1 (l)	FVC (l)	Po_2 (kPa)	Pco_2 (kPa)	Change in carboxy-haemoglobin (%)	Distance walked (m) breathing: Air	Oxygen	Air + CO	Oxygen + CO
1*	0·5	1·55	7·2	6·3	11·4	830	976	730	870
2	0·45	1·60	6·8	6·5	11·0	816	809	793	862
3	0·45	1·40	7·5	6·3	10·5	835	874	750	854
4	0·65	1·30	6·1	6·5	10·4	931	937	918	918
5	0·75	2·05	7·7	5·9	9·1	787	827	755	829
6	0·55	1·95	6·3	5·7	8·3	724	738	698	726
7*	0·55	1·25	6·7	5·6	8·7	336	378	210	279
8	0·55	1·20	7·1	5·9	9·8	725	800	714	772
9*	1·00	2·00	7·1	5·4	8·7	872	898	830	830
10	0·60	1·40	5·2	6·9	8·8	967	1006	903	955
11*	0·35	0·90	7·1	6·9	8·0	252	315	168	336
12*	0·50	1·60	6·5	7·6	8·7	1075	1187	1077	1182
13	0·60	2·10	7·3	6·1	8·5	347	555	326	527
14*	0·50	1·80	7·5	5·7	8·0	560	672	558	642
15	0·40	1·00	6·4	7·7	8·2	336	341	260	336
Mean±SD	0·56±0·16	1·54±0·4	6·83±0·65	6·33±0·7	9·2±1·1	694±263	754±258	646±280	728±257

*Patients known to be current smokers despite medical advice.
FEV_1 = Forced expiratory volume in one second. FVC = Forced vital capacity. Po_2 = Pressure of oxygen. Pco_2 = Pressure of carbon dioxide.
Conversion: SI to traditional units—Po_2 and Pco_2: 1 kPa ≈ 7·5 mm Hg.



Twelve-minute walking distance, with means ±SD, in 15 patients with chronic bronchitis and emphysema breathing different gas mixtures.
CO = Carbon monoxide.

breathing oxygen after the carboxyhaemoglobin concentration had been raised was significantly less than that walked when breathing oxygen before the concentration was raised ($p < 0.05$) but was not significantly different from that walked when breathing air before the concentration was raised ($p > 0.1$).

The average distance walked did not correlate with the resting arterial oxygen tension when patients were breathing air or with the ear oxygen saturation measured either before or at the end of exercising in the eight patients in whom this was measured. The reduction in distance walked after breathing carbon monoxide was not related to the normal smoking habits of the patients, since it occurred in both current smokers and ex-smokers. The heart rate at the end of the walk was 100-136 beats/minute, always higher than the 64-88 beats/minute at rest in each patient. The mean heart rate at the end of exercise, however, was not significantly different when air or oxygen was being breathed, before or after the carboxyhaemoglobin concentration was raised. In three of the six patients in whom an electrocardiogram was recorded at the end of the walk the ST segment was depressed by more than 1 mm, but ST depression was not correlated with breathing any particular gas or with a raised carboxyhaemoglobin concentration.

Discussion

Cigarette smokers are the non-industrial group most heavily exposed to carbon monoxide,[6] but the concentrations of carboxyhaemoglobin in smokers are not considered to produce symptoms. Acute carbon monoxide poisoning produces symptoms such as headache, vomiting, and coma only when the carboxyhaemoglobin concentration is over 35%. It has been suggested, however, that chronic exposure to carbon monoxide is associated with subtler changes in neurological function including an impaired ability to distinguish between short intervals of time, which is present even at low carbon monoxide concentrations.[7] The carboxyhaemoglobin concentrations reached in our studies are less than those that reduce maximal oxygen uptake in normal subjects[3] but above those that reduce the duration of bicycle ergometer exercise in patients with obstructive airways disease.[8] The 12-minute walking distance is a simple and reproducible test that correlates well with other subjective and objective variables of exercise tolerance[9,10] but is similar to the daily activities that are within the ability of these disabled patients.

We found that raising the carboxyhaemoglobin concentration from values found in non-smokers to values seen in patients who are moderate to heavy smokers reduced the distance that patients with hypoxic chronic bronchitis and emphysema could walk in 12 minutes. We confirmed that breathing 2 l oxygen/minute by nasal prongs can increase the distance walked by such patients[11] and that this effect of oxygen persists after the carboxyhaemoglobin concentration is raised. The benefit of oxygen on exercise when the carboxyhaemoglobin concentration is raised, however, is less than that before the concentration is raised, and the distance walked when breathing supplementary oxygen at a high carboxyhaemoglobin concentration is not significantly different from that covered when breathing air at the low concentration.

Changes in the oxygen content and oxygen-carrying capacity of the blood are thus associated with measurable changes in everyday exercise in these hypoxic patients. Similar increments in carboxyhaemoglobin concentration in healthy subjects do not affect oxygen delivery to exercising muscles as the cardiac output is increased to compensate. Carbon monoxide, however, reduces the maximal oxygen uptake in healthy people.[3] There was a considerable variation in the distance walked by different patients, not all of whom showed a dramatic change when the carboxyhaemoglobin concentration was increased (figure). In the eight patients in whom ear oxygen saturation was measured this fell by 3-10% (mean 6·3%) after exercise when breathing air and by 5-18% (mean 7·6%) after exercise when breathing air with a raised carboxyhaemoglobin concentration. The fall in arterial oxygen saturation, however, was not related to the distance walked. This variable response may arise from different degrees of physical fitness or from different limitations in the cardiac output response to exercise, so that the delivery of oxygen to the exercising muscle could not be maintained in all patients when the carboxyhaemoglobin concentration was raised.

These studies have shown that continued smoking may play a direct part in the reduction of exercise tolerance seen in patients with severe chronic bronchitis and emphysema. Furthermore, the resultant raised carboxyhaemoglobin concentration would negate any benefit on exercise from treatment with portable oxygen in such patients. Thus even patients with advanced hypoxic chronic bronchitis and emphysema may derive benefit from giving up smoking with a reasonable expectation of an increased exercise tolerance.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Bronchodilator reversibility testing in chronic obstructive pulmonary disease

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Background: A limited or absent bronchodilator response is used to classify chronic obstructive pulmonary disease (COPD) and can determine the treatment offered. The reliability of the recommended response criteria and their relationship to disease progression has not been established.
Methods: 660 patients meeting European Respiratory Society (ERS) diagnostic criteria for irreversible COPD were studied. Spirometric parameters were measured on three occasions before and after salbutamol and ipratropium bromide sequentially or in combination over 2 months. Responses were classified using the American Thoracic Society/GOLD (ATS) and ERS criteria. Patients were followed for 3 years with post-bronchodilator FEV_1 and exacerbation history recorded 3 monthly and health status 6 monthly.
Results: FEV_1 increased significantly with each bronchodilator, a response that was normally distributed. Mean post-bronchodilator FEV_1 was reproducible between visits (intraclass correlation 0.93). The absolute change in FEV_1 was independent of the pre-bronchodilator value but the percentage change correlated with pre-bronchodilator FEV_1 (r=–0.44; $p<0.0001$). Using ATS criteria, 52.1% of patients changed responder status between visits compared with 38.2% using ERS criteria. Smoking status, atopy, and withdrawing inhaled corticosteroids were unrelated to bronchodilator response, as was the rate of decline in FEV_1, decline in health status, and exacerbation rate.
Conclusion: In moderate to severe COPD bronchodilator responsiveness is a continuous variable. Classifying patients as "responders" and "non-responders" can be misleading and does not predict disease progression.

Chronic obstructive pulmonary disease (COPD) is currently defined by the presence of airflow limitation, measured by the forced expiratory volume in 1 second (FEV_1), that shows little or no improvement after inhaled bronchodilator drugs.[1–3] Selection of the maximum change in FEV_1 compatible with a diagnosis of COPD has proved difficult, but could be important clinically. Approximately 10% of patients with COPD show a short term spirometric "response" to a course of oral corticosteroids[4] that is maintained during subsequent inhaled corticosteroid treatment.[5] This is most likely to occur in those patients with a substantial (>400 ml) improvement in FEV_1 after oral corticosteroids.[6] A positive bronchodilator response may define a different natural history,[7 8] while European regulators now require that COPD patients included in treatment trials meet the European Respiratory Society (ERS) definition of irreversible disease. Bronchodilator testing can therefore have both clinical and regulatory importance.

Several criteria have been proposed to define a significant bronchodilator response.[9] Each has tried to encompass the known variability in FEV_1 measurements between and within days[10] by including a threshold value to reduce the risk of a chance finding. However, the approaches adopted differ. The American Thoracic Society (ATS) and the Global initiative for Obstructive Lung Disease (GOLD) both use a change of >12% of the baseline if this also exceeds 200 ml,[11 12] while the ERS recommends a change that is >9% of the predicted FEV_1.[13] Many reports simply quote a percentage change from baseline, which varies between 12 and 20%.[14] The reliability of these definitions has been challenged previously by data from the IPPB study[15] and in primary care where the patients studied had relatively mild disease and the stability of the categorisation was not assessed.[9] Direct comparisons between the different criteria and the effect of adding other bronchodilator drugs on the subsequent response rate have not been reported in large numbers of stable patients with moderate to severe COPD. Other factors such as smoking status, atopy, or changes in treatment may also influence the likelihood of a response.[16]

To determine whether routine bronchodilator testing is a robust measurement in individual patients already classified as having "poorly reversible" COPD, we examined data from the pre-randomisation phase of the ISOLDE (Inhaled Steroids in Obstructive Lung Disease) study.[17] We hypothesised that the number of patients classified as reversible would be influenced by spontaneous variation in airway calibre and by the use of additional test drugs, regardless of the choice of threshold for reversibility. We also tested the effect of atopy, smoking status, or the withdrawal of inhaled corticosteroids on the response to inhaled bronchodilators. Finally, we tested the hypotheses that the size of the bronchodilator response predicted the subsequent rate of decline in FEV_1, health status, or exacerbation rate over the following 3 years.

METHODS

Patients were recruited from the outpatient clinics of 18 UK hospital centres. All had a clinical diagnosis and symptoms compatible with non-asthmatic COPD and met both the ERS and ATS[1 2] spirometric criteria for this disorder. All were aged 40–75 years and were current or ex-tobacco smokers. Their baseline post-salbutamol FEV_1 was at least 0.8 l but <85% predicted and all had a ratio of FEV_1 to forced vital capacity (FVC) of <70%. At the first visit we excluded from further follow up those patients whose FEV_1 improved after inhaled salbutamol by more than 10% of their predicted FEV_1. Other exclusion criteria included the use of β adrenergic blockers, regular oral corticosteroids, or co-morbidities likely to reduce life expectancy below 5 years. Nasal and ophthalmic

Table 1 Demographic and lung function characteristics of study subjects

	N	Mean (SD)
Patients with complete data	660	
Pre-salbutamol FEV_1 (l)	660	1.28 (0.46)
Pre-salbutamol FEV_1 (% predicted)	660	45.5 (14.9)
Pre-salbutamol FVC (l)	660	2.94 (0.76)
Pre-salbutamol FEV_1/FVC	660	0.43 (0.11)
TLCO (mmol/min/kPa)*	556	4.91 (2.10)
Age (years)	660	63.8 (7.0)
Pack years smoked	615	44.6 (32.4)
Current smokers/ex-smokers	314/345	48%/52%
M/F	497/163	75%/25%
Atopic/non-atopic	175/485	27%/73%
Previous use of regular inhaled steroids (yes/no)	353/307	53%/47%

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; TLCO=carbon monoxide transfer factor.
*Normal range 10.84 (2.52) mmol/min/kPa.

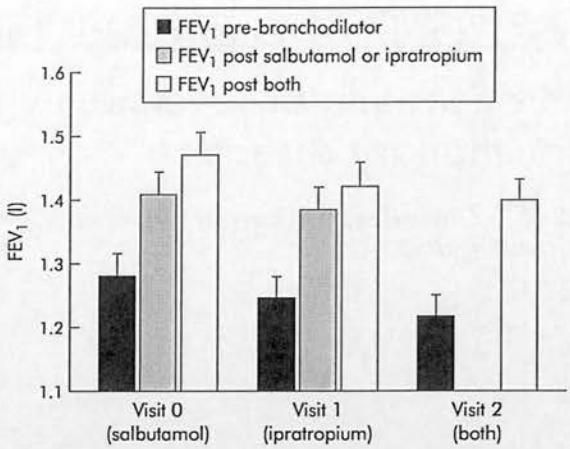

Figure 1 Mean (SE) FEV_1 before and after salbutamol, ipratropium, and the combination on three occasions at monthly intervals. Note the differences in pre-bronchodilator values between visits and the lack of change in post-bronchodilator FEV_1 after the combination at visits 1 and 2.

corticosteroids, theophyllines, other oral bronchodilators, and any inhaled bronchodilators were allowed. All patients gave their written informed consent before the study, which was approved by the local ethical committees of the participating institutions.

Measurements

All spirometric measurements were made using identical rolling seal spirometers (Sensormedics 2130D, BV Warwickshire, UK). Forced expiratory manoeuvres were performed in a standardised fashion[13] and the best FEV_1 and FVC recordings within 50 ml of each other were accepted. We developed an intra-centre and inter-centre quality control protocol based on the criteria used in the Lung Health Study.[18] These were modified to accept an FVC in which a volume change of <40 ml in a 2 second period was not required provided that the forced expiratory time exceeded 12 seconds. Each spirometric recording was reviewed centrally and the percentage of tests meeting the external quality control criteria was fed back to the study centre to ensure high quality data throughout the study. Patients were asked to omit short acting inhaled bronchodilators for 4 hours before attendance, and long acting oral and inhaled agents for 12 hours. If the patient experienced a respiratory tract infection or exacerbation of COPD requiring treatment in the 4 weeks before their clinic visit, this was re-scheduled to provide valid spirometric testing.

Smoking status was assessed using exhaled breath carbon monoxide (CO) measured after a 20 second breath hold using a mini Smokerlyzer (Bedfont Technical Instruments Ltd, Kent, UK). Urinary cotinine was measured by thiocyanate assay in all patients during the run-in and subsequently in patients who claimed not to be smoking but had an expired CO level of >8 ppm. Self declared non-smokers were classified as smokers if their urinary cotinine concentration was >40 mg/ml and expired CO was >10 ppm or if the urinary cotinine value was missing but the expired CO was >10 ppm on more than two visits.

Atopic status was assessed objectively by skin prick testing to four common allergens (*Aspergillus fumigatus*, *Dermatophagoides pteronyssinus*, cat dander, and mixed grass pollen) together with a positive and negative control. Individuals were considered to be atopic if they reacted with a wheal of more than 3 mm in diameter to more than one of these allergens. Testing for atopy was conducted at the time of the first attendance.

Study protocol

Patients attended on three occasions at 4 weekly intervals before treatment randomisation. On the first occasion (V0) they performed spirometric tests, then received 400 µg salbutamol via a large volume spacer (Volumatic) and spirometric tests were repeated after 30 minutes. Ipratropium bromide 80 µg was then given via the spacer and spirometric tests were repeated 30 minutes later. At the next attendance (V1) the order of the drugs was reversed, while on the third visit (V2) salbutamol inhalation was immediately followed by ipratropium and spirometric testing at 30 minutes. After V2, patients were randomised to receive either fluticasone 500 µg twice daily via the spacer or an identical placebo. They attended 3 monthly for repeat spirometric testing as described at V2 until 3 years of follow up had been completed or they had withdrawn from the study.

Data analysis and statistical methods

The change in spirometric values after bronchodilation were expressed as: (a) absolute change (ml); (b) percentage change from baseline; and (c) change in percentage predicted normal values. Spirometric values for the normal population used the ECCS formulae.[13]

Student's *t* tests were used to test differences from baseline and differences in mean values between visits. FEV_1 repeatability was measured using the intraclass correlation coefficient. The relationship between pre-bronchodilator values and bronchodilator response was estimated using regression coefficients.[19] Interactions with smoking status, sex, and atopy were investigated using analyses of covariance. The rate of decline in FEV_1 was derived using the placebo data set only and was expressed as the change in post-bronchodilator FEV_1 (ml) per year. These data were analysed using a random coefficients mixed effects model as described by Burge *et al*.[17] Similarly, data for the change in health status with time and the exacerbation rate were collected and analysed as described in detail by Burge *et al*.[17] All tests were two sided with a 5% level of significance. Data are expressed as mean (SE) unless otherwise stated.

RESULTS

Study population

Of the 990 patients fulfilling the entry criteria, 751 completed the 2 month run-in and were randomised, 375 receiving placebo. Of the randomised population, 54% had used regular inhaled corticosteroids before the study. Complete data at all three bronchodilator assessments were available for 660 patients. The loss of data in the remaining 91 patients was largely due to delayed assessment because of respiratory tract

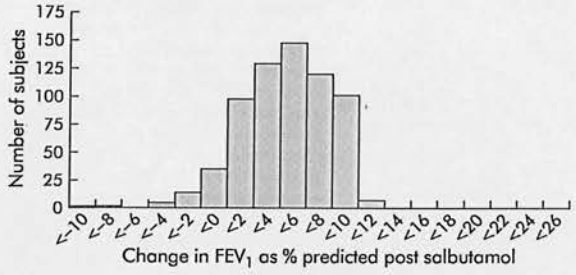

Figure 2 Histograms of the distribution of bronchodilator response seen in data derived at visit 0 after salbutamol alone.

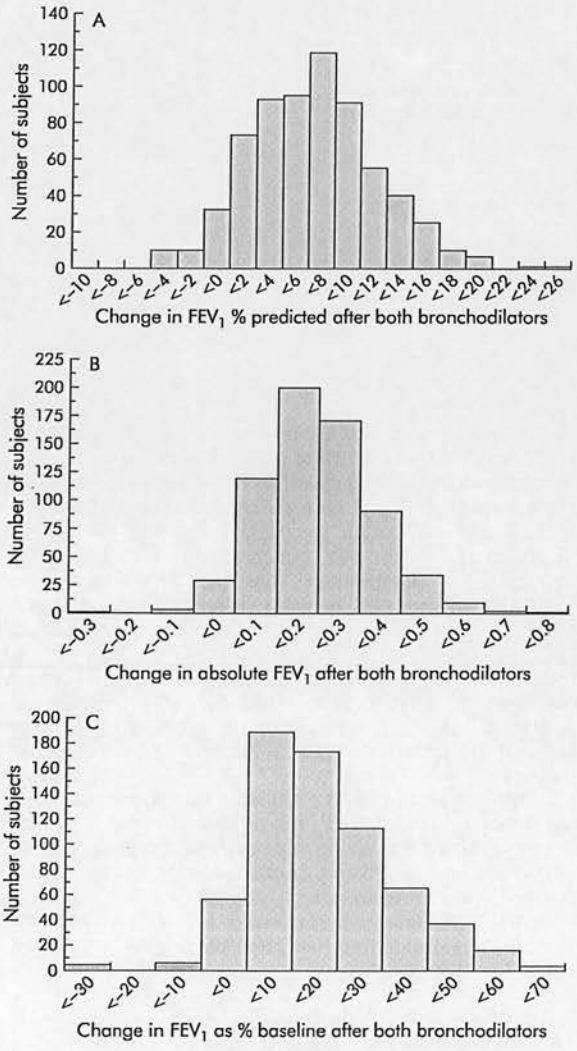

Figure 3 Data at the same visit as fig 2 but after salbutamol and ipratropium and expressed as (A) percentage of predicted FEV_1, (B) absolute change in FEV_1, and (C) percentage change from baseline.

infections; these patients did not differ significantly in any baseline characteristic or prior treatment from those who are reported here. Details of the study population are presented in table 1 based on measurements made at V0.

Response to bronchodilator drugs

FEV_1 and FVC both increased significantly after inhaled salbutamol at V0 (mean change in FEV_1 128 (4) ml, mean change

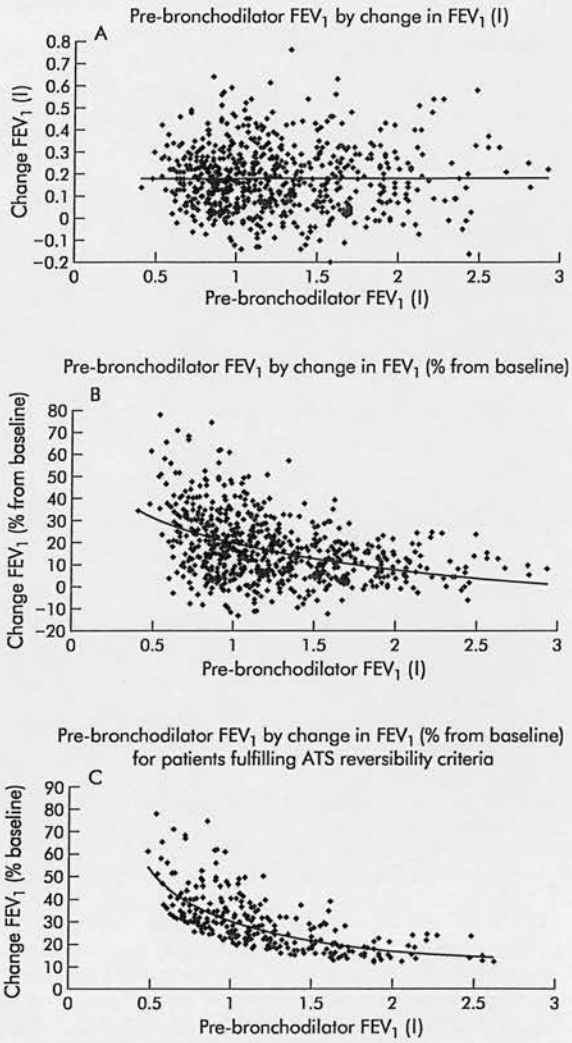

Figure 4 Relationship between the response to bronchodilator and the pre-bronchodilator FEV_1 at visit 2. (A) Absolute change in FEV_1 is unrelated to initial FEV_1. (B) Change as a percentage of baseline FEV_1 is related to initial FEV_1 in a curvilinear fashion which persisted even when the ATS absolute volume criteria were included (C).

in FVC 286 (12) ml). A further significant increase in both variables occurred after ipratropium (fig 1). The pre-bronchodilator FEV_1 at V1 was lower than at V0 ($p<0.0001$), and the increase in FEV_1 after ipratropium (the first drug given at V1) was larger than when salbutamol was given first at V0. The change in FEV_1 when ipratropium was added to salbutamol at V0 was 63 (4) ml, and the change when salbutamol was added to ipratropium at V1 was 39 (4) ml (difference 24 ml, $p<0.0001$). There were no significant differences in the mean post-bronchodilator FEV_1 between V1 and V2 or in the mean bronchodilator response at any visit. The intraclass correlation coefficient for pre-bronchodilator FEV_1 was 0.91 and for post-bronchodilator FEV_1 was 0.93 for the three visits.

The distribution of the change in FEV_1 expressed as a percentage of predicted after salbutamol was censored by our inclusion criteria (fig 2). The distribution became more obviously normal when data after both salbutamol and ipratropium were plotted (fig 3A). Similar patterns were seen when the absolute change in FEV_1 and percentage change from baseline were used, although the latter group were skewed towards apparent responsiveness (fig 3B and C).

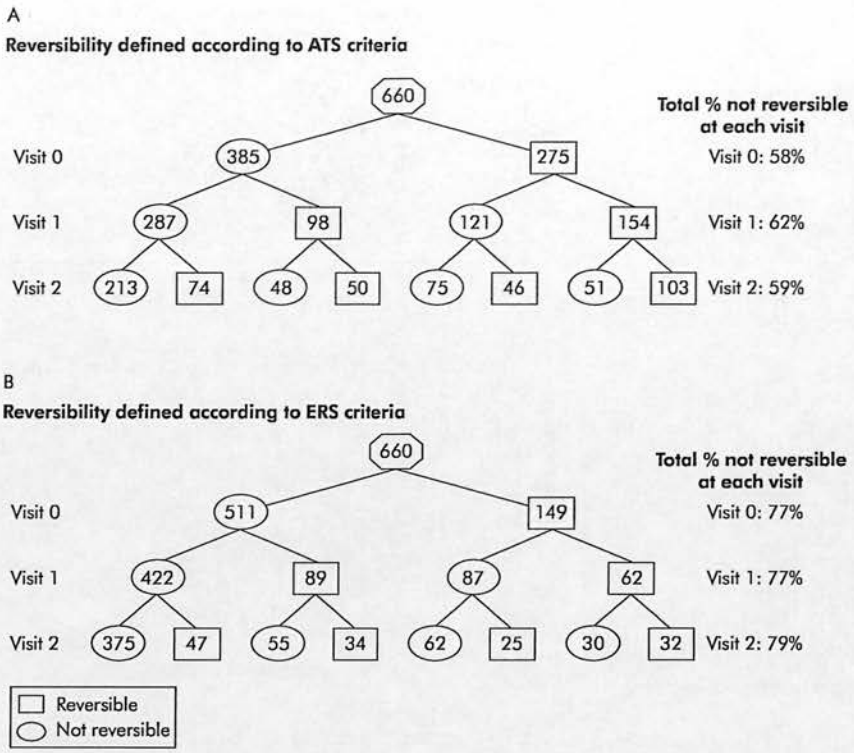

Figure 5 Changes in responder classification and corresponding subgroup mean FEV_1 at each visit after both bronchodilators using (A) American Thoracic Society and (B) European Respiratory Society criteria. Numbers in circles refer to the total classified as positive responders at that visit and those in squares are the non-responders on the same occasion. Note that some patients in the ERS criteria group exhibited a "response" after both drugs at the first visit despite being classified as non-responsive to salbutamol alone.

Influence of baseline FEV_1 on likelihood of being classified as responsive

The relationships between the pre-bronchodilator FEV_1 and the size of the bronchodilator response expressed in different ways are shown in fig 4 using data from V2. The change in FEV_1, whether expressed as an absolute value or as a percentage of predicted, was uninfluenced by the pre-bronchodilator FEV_1 when measured in absolute units. When the data were expressed as a percentage change from baseline there was a clear curvilinear relationship with the pre-bronchodilator FEV_1, best described using a power function ($r=0.17$, $p<0.0001$). This relationship persisted ($r=0.44$, $p<0.0001$) even when patients whose FEV_1 changed by less than 200 ml were excluded (fig 4C).

Reproducibility of the response

The reliability of the patient's responder classification is shown in fig 5 using data obtained following both bronchodilator drugs. Using the ATS classification, only 103/275 (37%) of those initially classified as reversible remained so on the two subsequent visits while 213/385 (55%) of those classified as irreversible showed equally inconsistent results. Comparable figures for the ERS classification were 32/149 (21%) initially classified as reversible and 375/511 (73%) as irreversible. Overall, 52% of patients classified by ATS criteria and 253/660 (38%) classified using ERS criteria would be reclassified if tested on a different occasion. There was a significant association ($p<0.0001$) between the change in pre-bronchodilator FEV_1 between visits and the change in response classification—that is, an increase in pre-bronchodilator FEV_1 between visits was likely be associated with reclassification to being irreversible and, conversely, a fall in pre-bronchodilator FEV_1 between visits led to reclassification as reversible. Patients identified as being consistently reversible by ATS and ERS classifications are compared in table 2. There were no significant differences between these groups in the numbers of smokers and atopic subjects.

Using data obtained at V2 following both bronchodilators, the absolute change in FEV_1 was unrelated to smoking status or atopy. There were no sex differences in the magnitude of response to bronchodilators. In this study 53% of the population had inhaled corticosteroids withdrawn at screening but there was no difference in the change in FEV_1 at V2 between these patients and those who had not previously received inhaled corticosteroids.

Table 2 Demographic characteristics of patients consistently reversible and irreversible using ATS and ERS criteria

	ATS response (n=103)	ATS no response (n=213)	Difference (p value)	ERS response (n=32)	ERS no response (n=375)	Difference (p value)
Post-bronchodilator FEV_1 (l)	1.60 (0.04)	1.35 (0.03)	<0.0001	1.70 (0.07)	1.37 (0.02)	<0.0001
Change in FEV_1 (l)	0.34 (0.01)	0.09 (0.01)		0.37 (0.02)	0.13 (0.01)	
Change in FEV_1 (% predicted)	11.17 (0.29)	3.60 (0.21)		13.13 (0.48)	4.60 (0.17)	
% women	12	38	<0.0001	25	24	0.9
% smokers	48	47	>0.9	47	48	0.9
% atopic	32	24	0.1	28	24	0.6
% previous regular ICS	61	51	0.1	66	51	0.1

Values are mean (SE).
FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroids.

Bronchodilator response as a predictor of subsequent disease progression

The mean rate of decline in FEV_1 in placebo treated patients was 53 ml per year. We found no relationship between the absolute or percentage predicted changes in FEV_1 after bronchodilator and the subsequent rate of decline in FEV_1 in our model which controlled for the baseline post-bronchodilator data. The mean rate of decline in health status was unrelated to baseline bronchodilator response ($p=0.4$). Bronchodilator response was divided into responders and non-responders by the median value (170 ml). Decline in health status was not significantly different between the two groups (responders 2.8 units/year; non-responders 3.4 units/year; $p=0.3$). The annual rate of exacerbations was not significantly different between the two groups (responders 1.5 exacerbations/year; non-responders 1.5 exacerbations/year; $p=0.6$).

DISCUSSION

COPD is now defined using the combination of a clinical history and objective evidence of airflow limitation. Data from this study show that these criteria identify patients with an accelerated rate of decline in FEV_1. However, the distinction from chronic asthma with limited reversibility remains difficult, and most treatment guidelines use the spirometric response to a bronchodilator drug to aid the diagnosis and, in some cases, to make recommendations about treatment decisions.[12] Previous studies have examined the ability of bronchodilator testing to differentiate between asthma and COPD in milder disease and have found no clear distinction spirometrically between the two.[9 20] This has not prevented these criteria being widely recommended in the assessment of more severe COPD or in the selection of patients for inclusion in treatment trials.[17 21] In this study we examined the reliability of the bronchodilator response in moderate to severe COPD defined as "poorly reversible" disease by one set of criteria and have related it to clinically relevant outcomes. Our data suggest that the current definitions of bronchodilator reversibility have significant limitations in established COPD and may be potentially misleading.

As in the EUROSCOP trial,[22] we selected patients with a $<10\%$ change in predicted FEV_1 after an inhaled β agonist. The distribution of bronchodilator responses using this criterion was censored but returned towards normal once the second bronchodilator drug was added. In these patients we could not identify a separate population of more responsive patients however the data were expressed.

Using a second drug, whether ipratropium or salbutamol, increased the mean FEV_1 and changed the number of patients classified as reversible. The group mean change in FEV_1 after each drug was reproducible between visits despite the significant fall in pre-bronchodilator FEV_1 which was probably related to both the withdrawal of inhaled corticosteroids and regression to the mean.[23] The post-bronchodilator FEV_1 values were highly correlated between visits, supporting the use of this measurement as the principal outcome in longitudinal studies of the evolution of the disease.

Neither the American nor European definitions were acceptably reproducible. Over half the patients initially classified as reversible by the ATS/GOLD definition would be reclassified had they attended on another occasion. Likewise, 38% of those classified by the European criteria changed their apparent responder status with time, despite all being irreversible to salbutamol alone at the first visit.

A further problem with the ATS and GOLD definitions, but not with those based on an absolute or percentage predicted change, is their dependence on the baseline FEV_1 even when an initial absolute value of 200 ml is considered a threshold for this measurement (fig 4C). This may suggest that a substantial degree of reversibility is present even when the absolute increase in FEV_1 is similar to that seen in less severe disease. The absolute changes in FEV_1 we saw were similar to that in much milder disease in the Lung Health Study.[18]

Our data were uninfluenced by differences in sex, current smoking status, atopic status, or the prior use of inhaled corticosteroids. Neither smoking status nor atopy were over-represented in the patients who showed the most "consistent" positive responses, suggesting that improvement in lung function in COPD does not correspond to either an asthmatic or ex-smoking phenotype. Patients treated previously with inhaled corticosteroids did not differ in their bronchodilator responses from those not so treated. The most likely explanation for the between day variation in classification is the effect of small fluctuations in bronchomotor tone as shown by the inverse relationship between pre-bronchodilator FEV_1 and the chance of a change in responder classification. Similar fluctuations in airway calibre have been noted in other COPD populations and have been related to the degree of cholinergic tone in the airway smooth muscle.[6 24]

Our model of the rate of decline in FEV_1 controlled for the post-bronchodilator FEV_1 value obtained during the run-in period. We found no evidence for a relationship between the change in FEV_1 after bronchodilators, however expressed, and the rate of decline in lung function. We confined our analysis to the placebo treated patients to exclude any confounding effects of the inhaled corticosteroids. Our data contrast with those obtained from a more mixed population where only partial analysis of the FEV_1 decline was available.[7] It emphasises the difficulty of using measures like a bronchodilator "response" in patients with more severe and structurally determined airflow limitation. Our results are in keeping with a long term Danish population study where COPD mortality was related to both pre-bronchodilator FEV_1 and the change in FEV_1 at study entry, but the latter variable was no longer significant when the relationship was expressed in terms of the post-bronchodilator value.[25] The failure of the response to predict future changes in health status or exacerbation frequency is not surprising given the limitations of this measurement.

We could not, for logistic reasons, include a group receiving placebo inhalations but felt that the reproducibility of the FEV_1 which this assesses has been reported sufficiently frequently to make this unnecessary.[10 13] The doses of the bronchodilator drugs may not have been maximal[26 27] or optimally timed, but these minor differences are unlikely to have systematically affected our results. This study specifically addressed the usefulness of classifying patients who are believed to have COPD on their response to one dose of one bronchodilator, a common clinical situation. The conclusion that this is a continuously distributed response susceptible to the number of drugs used and day of testing suggests that, even in this group of patients, identifying responder status in this way is of little practical value. We cannot address whether this would be true for those with a more substantial bronchodilator response, but the variability in the tail of our response distribution suggests that it may also be true in these cases.

Our data are not surprising given the day to day variation in bronchomotor tone and the arbitrary nature of the definitions adopted. Unfortunately, many clinicians still rely on these responses to decide whether patients have COPD and what treatment they should receive, while regulators in Europe and North America take very different views about the inclusion of reversibility data in clinical treatment trials. A major purpose of this study has been to alert them and the regulatory authorities to the significant limitation of any classification currently in use. This variability in classification helps to explain the unreliability of bronchodilator responsiveness as a predictor of improvement after treatment.[28 29] If bronchodilator response data are to be presented in COPD, then the absolute change in FEV_1 should be reported without making prior assumptions about its diagnostic significance.

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Bronchodilator reversibility testing in chronic obstructive pulmonary disease

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Alternative methods for assessing bronchodilator reversibility in chronic obstructive pulmonary disease

J Hadcroft, P M A Calverley

Abstract

***Background*—Bronchodilator reversibility testing is recommended in all patients with chronic obstructive pulmonary disease (COPD) but does not predict improvements in breathlessness or exercise performance. Two alternative ways of assessing lung mechanics—measurement of end expiratory lung volume (EELV) using the inspiratory capacity manoeuvre and application of negative expiratory pressure (NEP) during tidal breathing to detect tidal airflow limitation—do relate to the degree of breathlessness in COPD. Their usefulness as end points in bronchodilator reversibility testing has not been examined.**

***Methods*—We studied 20 patients with clinically stable COPD (mean age 69.9 (1.5) years, 15 men, forced expiratory volume in one second (FEV_1) 29.5 (1.6)% predicted) with tidal flow limitation as assessed by their maximum flow-volume loop. Spirometric parameters, slow vital capacity (SVC), inspiratory capacity (IC), and NEP were measured seated, before and after nebulised saline, and at intervals after 5 mg nebulised salbutamol and 500 µg nebulised ipratropium bromide. The patients attended twice and the treatment order was randomised.**

***Results*—Mean FEV_1, FVC, SVC, and IC were unchanged after saline but the degree of tidal flow limitation varied. FEV_1 improved significantly after salbutamol and ipratropium (0.11 (0.02) l and 0.09 (0.02) l, respectively) as did the other lung volumes with further significant increases after the combination. Tidal volume and mean expiratory flow increased significantly after all bronchodilators but breathlessness fell significantly only after the combination treatment. The initial NEP score was unrelated to subsequent changes in lung volume.**

***Conclusions*—NEP is not an appropriate measurement of acute bronchodilator responsiveness. Changes in IC were significantly larger than those in FEV_1 and may be more easily detected. However, our data showed no evidence for separation of "reversible" and "irreversible" groups whatever outcome measure was adopted.**

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Keywords: chronic obstructive pulmonary disease; bronchodilator; reversibility; end expiratory lung volume; flow limitation

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Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation which varies little over several months of observation or after treatment.[1 2] The assessment of airflow limitation usually relies on spirometric testing and, in particular, the forced expiratory volume in 1 second (FEV_1) which is the usual outcome measure in diagnostic bronchodilator reversibility testing.[3] Although useful diagnostically and prognostically,[4] spirometric abnormalities are poor descriptors of the severity of breathlessness in COPD.[5] Likewise, significant changes in FEV_1 after inhaled bronchodilators are not necessary for improvement in exercise performance or dyspnoea to occur.[5–7] Two alternative techniques of measuring lung mechanics relatively easily are now available. Both are better correlates of breathlessness than FEV_1, but their reproducibility and sensitivity to change in response to bronchodilator drugs has not been assessed—an important consideration if they are to be of practical value.

The application of negative expiratory pressure during tidal breathing (the NEP technique) is a simple and rapid way of assessing the presence of flow limitation during tidal respiration which overcomes the problems of gas compression artefacts and variations in the preceding volume history of the manoeuvre.[8] The degree of tidal flow limitation correlates with the severity of everyday breathlessness using the MRC scale.[9] One study has reported that tidal flow limitation was unchanged after a moderate (400 µg) dose of inhaled salbutamol in patients with resting flow limitation,[10] but the effects of higher doses of this drug or other bronchodilators have not been examined.

Pulmonary hyperinflation during spontaneous breathing is common in advanced COPD, relates well to the intensity of dyspnoea during exercise,[11] and can be reproducibly detected using the inspiratory capacity manoeuvre.[12] Inhaled β agonists and anticholinergic agents reduce exercise induced dynamic hyperinflation.[6 7] Measurements of expired lung volume such as the forced and relaxed vital capacities also improve after bronchodilators, suggesting a fall in residual volume, but how these changes relate to those in inspiratory capacity (IC) is less certain.

The major diagnostic difficulties with spirometric based reversibility testing occur in patients with a low baseline FEV_1 where changes after the bronchodilator drug fall within the spontaneous reproducibility of the

measurement.[13] In these individuals hyperinflation is present at rest and tidal flow limitation is more likely to be present when the subject is seated,[8] increasing the chance of a positive signal using these variables after a bronchodilator test. Our previous studies have suggested that acute bronchodilator responsiveness in COPD is a continuous variable.[14] We hypothesised that changes in the degree of hyperinflation and in tidal flow limitation would be as reproducible as those in FEV_1 and would separate potential responder groups for future treatment trials. To test this, we have conducted a single blind randomised placebo controlled trial of nebulised β agonists and anticholinergic drugs measuring both pulmonary hyperinflation and tidal flow limitation in a group of patients with more severe COPD than reported previously. Additionally, we have measured the relaxed or "slow" vital capacity to assess whether this more readily available measurement showed equivalent sensitivity to change after active drugs to those seen with the newer measurements of resting lung mechanics.

Methods

SUBJECTS

Twenty patients (15 men) with severe COPD participated in the study. All had been cigarette smokers of >20 pack years, had a clinical course consistent with the disease, and met the BTS criteria for diagnosis and classification of disease severity.[15] None had clinical or radiographic evidence of bronchial asthma, bronchiectasis, or neoplasia, nor of significant cardiovascular/neuromuscular disease which would affect their resting sensation of breathlessness or their pulmonary function results. All had been free of respiratory tract infection for at least 4 weeks. Short acting inhaled bronchodilators were omitted for 6 hours, long acting inhaled bronchodilators were omitted for 12 hours, and oral theophyllines were omitted for 24 hours prior to testing and caffeinated beverages were avoided for 6 hours. All were recruited from the respiratory outpatient clinics of the University Hospital Aintree and gave their informed consent to the study which was approved by our institutional ethics committee.

PROTOCOL

Each patient attended the Pulmonary Physiology Laboratory on two occasions at the same time of day. At the first visit they were randomly allocated to one of two groups, A or B, to determine the order in which they would receive their bronchodilator drugs. They completed a St George's Respiratory Questionnaire to assess their health status[16] and resting arterial blood gas tensions were measured seated breathing room air. At each attendance spirometric parameters were recorded after the patient had been sitting quietly for at least 5 minutes, followed by measurement of IC and slow vital capacity (SVC), mean inspiratory and expiratory mouth pressures, thoracic gas volume, resting breathing pattern, and finally NEP testing (see below). Before each test period the intensity of breathlessness was graded using a modified Borg category scale[17] in response to the question: "How breathless are you feeling?" Each patient received 2.5 ml normal saline via a wet nebuliser (Sidestream Disposable Nebuliser, MedicAid Ltd, UK) at flow rate of 5 l/min for 5 minutes. After 15 minutes' rest this assessment protocol was repeated. Patients in group A were then given 5 mg salbutamol via the nebuliser at the same flow rate as the saline. After a further 15 minutes all measurements were repeated. Group A subjects finally received 500 μg ipratropium bromide nebulised as before and then repeated their measurements 45 minutes later. Patients in Group B received saline, followed by nebulised ipratropium with measurements made after 45 minutes, then nebulised salbutamol with final measurements made 15 minutes after this.

On the second day the same protocol was followed but the order of the bronchodilators was reversed.

PHYSIOLOGICAL MEASUREMENTS

Spirometry

FEV_1 and forced vital capacity (FVC) were measured using a 1 litre dry rolling seal spirometer (MedGraphics, Minnesota, USA), the best FEV_1 and FVC values from reproducible measurements being reported as recommended by the ATS.[18 19] Normal values were those of the ECSC.[20] At the time of their first visit a maximum flow-volume manoeuvre was recorded after a period of quiet breathing and with the equipment software a tidal loop was positioned relative to the maximal loop using the IC manoeuvre. The resulting plot was printed to determine whether the resting tidal loop exceeded the maximum flow-volume envelope.

Inspiratory capacity/slow vital capacity

These were measured using the same spirometer as above. After four normal tidal breaths the patient inhaled to total lung capacity (TLC) from their spontaneous end expiratory lung volume (EELV), paused for 1 second, then exhaled slowly to functional residual capacity. This manoeuvre was repeated until two values corresponded to within 5% of each other.

Thoracic gas volume/total lung capacity

These were measured in the MedGraphics constant volume body plethysmograph and required subjects to pant against a closed mouthpiece supporting their cheeks. Thoracic gas volume and TLC were calculated using the commercial software supporting this equipment. Knowing the TLC, the EELV could be determined from the equation:

$$EELV = TLC - IC$$

Mean inspiratory and expiratory mouth pressures

These were measured according to the method of Black and Hyatt.[21] Three measurements of each were made and the best of the three recorded.

BREATHING PATTERN

After 3–4 minutes of stable breathing a 30 second period of tidal breathing was recorded on

the NEP circuit (Raytech Instruments, Vancouver, Canada) (see below) and displayed on the computer screen. Inspiratory and expiratory times (Ti, Te), the total time cycle time (Ttot), and tidal volume (Vt) were measured using the customised software. The duty cycle (Ti/Ttot) and mean inspiratory and expiratory flows (Vt/Ti and Vt/Te) were derived from these data.

NEP METHOD FOR MEASURING EXPIRATORY FLOW LIMITATION

The testing method and the protocol used are similar to those described elsewhere.[8 9 22] The NEP circuit comprised a flanged mouthpiece in series with a pneumotachograph (Aeromech Devices, Ontario, Canada) and a Venturi device (Aeromech Devices), one end of which was open to the atmosphere, the other connected to the cone of the heated pneumotachograph (3700 series, Hans Rudolph Inc, Kansas City, USA). A side port on the Venturi device was connected via an electrically operated solenoid valve (Aeromech Devices) to a source of compressed air using rigid tubing. A pressure regulator connected to the source of compressed air could be adjusted to set the NEP to the required level of –5 cm H_2O. The solenoid valve was controlled by a computer (Raytech Instruments Inc, Vancouver, Canada) using customised software to activate the pressure source 0.2 seconds after the onset of expiration and to remain activated for a preset period. This period was equal to the length of tidal expiration of each individual subject. Airflow was measured from the pressure drop across the pneumotachograph screen using a differential pressure transducer (Raytech Instruments Inc) calibrated before each subject's visit with a water manometer. These signals were amplified, filtered, digitised, analysed, and displayed on a computer screen. Volume was obtained by numerical integration of the flow signal. Flow and volume could be continuously monitored on screen during the study, which permitted monitoring of breathing stability and timing of the NEP test. By constantly monitoring flow and volume, leaks could be identified visually.

Procedure

With the patient in a seated position with a nose clip in place, tidal breathing was recorded for 30 seconds after acclimatisation and the duration of tidal expiration was calculated. A series of test NEP breaths was performed using an NEP of –5 cm H_2O until the patient became accustomed to the procedure. Each NEP period was equal to the duration of the previous tidal expiration and was triggered 0.2 seconds after the onset of expiration. NEP was only applied once a steady state of tidal breathing was reached, and when air leaks could be confidently excluded.

Analysis of flow limitation was made by superimposing the expiratory limb of the flow-volume loop in the presence of NEP on the expiratory limb of the preceding breath. If flow could be increased by the application of NEP, then the patient was not flow limited. In preliminary studies we noted significant breath to breath variability in flow limitation in some subjects so only the first pair of breaths at each measurement was analysed. The degree of flow limitation was scored according to the amount by which the two expiratory limbs overlapped so that the period of flow limitation was expressed as a percentage of the control breath, as described elsewhere.[8] We then divided these percentages into three groups (0, 1, and 2) where 0 = no flow limitation at all during expiration (0%), 1 = partial flow limitation (>0% but <100%), and 2 = complete flow limitation (100%).

STATISTICAL ANALYSIS

Data are expressed as mean (SE) unless otherwise stated. Statistical analysis of the physiological measurements before and after saline, and each bronchodilator alone and in combination was made using analysis of variance (ANOVA). A p value of <0.05 was taken to be of statistical significance. Comparisons between the same variables on different occasions were made using the method of Bland and Altman. 95% agreement limits for each pulmonary function variable after placebo inhalation were calculated as previously described.[23] Comparisons between subgroups defined by flow limitation were made using analysis of variance while Borg dyspnoea scores were tested non-parametrically (Wilcoxon signed rank test).[24]

Results

DEMOGRAPHIC DATA

Demographic data for the patient population studied is shown in table 1. They were an elderly group with severe airflow limitation, significantly raised lung volumes, and markedly impaired health status. All individuals had tidal flow limitation which exceeded the maximum flow-volume envelope as measured in the body plethysmograph. However, on NEP testing when seated, eight individuals had no flow limitation, six had partial flow limitation, and six had complete flow limitation at rest. The demographic features of each of these subgroups are also shown in table 1. NEP testing was poorly reproducible when repeated within a few breaths of the first test. Only 12 individuals had a consistent degree of tidal flow limitation, which worsened in two and decreased in six. All subsequent NEP data are reported on the first breath results.

REPRODUCIBILITY

Short term reproducibility data are presented in fig 1 for the principal flow and volume measures in the form of Bland-Altman plots. These demonstrate relatively narrow 95% agreement limits with no evidence of a relationship between the baseline value and the reproducibility of the measurement. The mean (SE) between day reproducibility (mean of the differences between each of the baseline measurements on the two days of testing) of the FEV_1, FVC, IC, and SVC was 0.06 (0.01) l, 0.23 (0.04) l, 0.07 (0.04) l, and 0.16 (0.06) l, respectively. The mean change in TLC after

Table 1 Mean (SE) baseline demographic data for the 20 subjects with COPD studied

	All (n=20)	*NEP=0 (n=9)*	*NEP=1 (n=4)*	*NEP=2 (n=7)*
Age (years)	69.9 (1.5)	61.4 (7.4)	67.0 (2.0)	73.9 (1.9)
M:F	15:5	7:2	4:0	4:3
BMI (kg/m²)	24.7 (2.5)	25.5 (1.1)	21.6 (1.1)	25.4 (1.8)
FEV_1 (l)	0.78 (0.05)	0.96 (0.06)	0.61 (0.1)*	0.65 (0.06)*
FEV_1 (% predicted)	29.6 (2.3)	34.2 (2.4)	20.5 (2.5*)	28.9 (4.8)
FVC (l)	2.26 (0.13)	2.62 (0.19)	1.98 (0.18)	1.95 (0.19)*
FVC (% predicted)	64.6 (3.2)	71.4 (4.0)	51.3 (4.1)*	63.4 (5.7)
FEV_1/FVC (%)	35.5 (2.2)	37.6 (2.8)	30.8 (3.3)	35.4 (5.1)
IC (l)	1.65 (0.09)	1.9 (0.2)	1.5 (0.1)	1.4 (0.1)*
SVC (l)	2.65 (0.16)	3.0 (0.2)	2.5 (0.1)	2.3 (0.3)*
TLC (l)	7.48 (0.34)	7.5 (0.5)	8.5 (0.9)	6.9 (0.6)
Pao_2 (kPa)	8.75 (0.26)	9.3 (0.4)	8.3 (0.3)	8.3 (0.4)
$Paco_2$ (kPa)	5.52 (0.17)	5.3 (0.2)	5.6 (0.4)	5.8 (0.3)
SGRQ (%)	62.7 (3.3)	62.7 (5.2)	64.7 (7.9)	61.6 (5.9)

BMI = body mass index; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IC = inspiratory capacity; SVC = slow vital capacity; RLC = total lung capacity; Pao_2, $Paco_2$ = arterial oxygen and carbon dioxide tensions; SGRQ = St George's Respiratory Questionnaire; NEP = negative expiratory pressure; 0 = no flow limitation; 1 = partial flow limitation; 2 = complete flow limitation.
*p<0.05.

saline was 0.58 L with wide 95% confidence intervals (–2.04 to +1.79). The NEP data were less reproducible with 12 subjects remaining the same, four showing less tidal flow limitation, and four showing more tidal flow limitation on repeat testing on the second day. These changes showed no consistent relationship with measured IC or breathing pattern.

BRONCHODILATOR RESPONSE

Group mean (SE) bronchodilator responsiveness data are shown in fig 2A and compared with the changes after saline. Significant (p<0.001) increases in FEV_1 occurred after both salbutamol and ipratropium and a further significant increase (p<0.05) compared with the value after a single agent was seen when the two groups were combined, irrespective of the order in which they were given. This was also the case for IC (fig 2B). There were no significant differences in the magnitude of change after either drug given singly or in combination, irrespective of the different timings of the treatment. Similarly, significant changes in IC, FVC, and SVC were seen and similar changes occurred irrespective of the measure used to

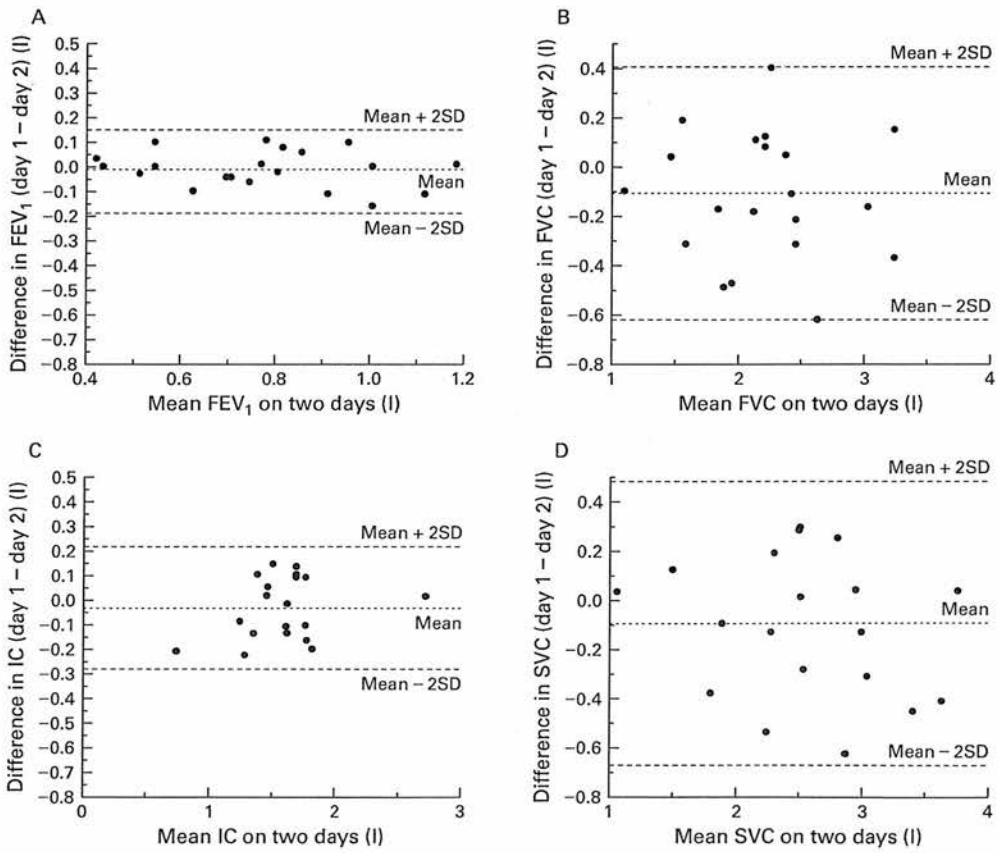

Figure 1 Bland-Altman plot of mean baseline values for each subject on two days plotted against the difference between the baseline values on the two days. Broken lines represent the mean and 2 standard deviations either side of the mean of the differences between baseline values. (A) forced expiratory volume in one second (FEV_1), (B) forced vital capacity (FVC), (C) inspiratory capacity (IC), (D) slow vital capacity (SVC). The 95% agreement limits for all measurements are narrow.

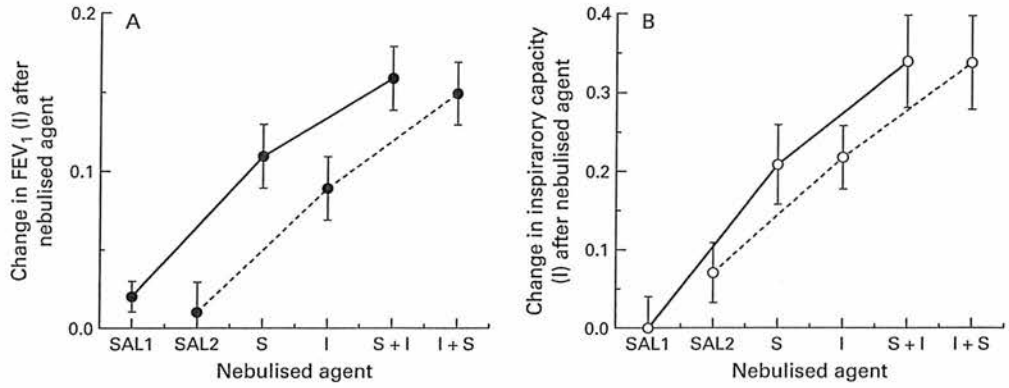

Figure 2 (A) Mean (SE) changes in forced expiratory volume in one second (FEV_1) after placebo and active drug, singly and in combination. SAL1 and SAL2 = saline (placebo) on days 1 and 2, respectively, S = salbutamol, I = ipratropium. Day 1 is the day on which salbutamol was the active drug which was given first (solid lines); day 2 is the day on which ipratropium was given first (broken lines). (B) Data for inspiratory capacity measured at the same time as the FEV_1 and with the same conventions.

assess them (table 2). The FEV_1/FVC and FEV_1/SVC ratios were not significantly changed after either saline or any bronchodilator given singly or in combination. The number of individuals exceeding the 95% confidence interval for the measurements after both bronchodilators are shown in fig 3 where FEV_1 and IC data are compared. Using a change of 12% baseline as representing reversible disease, on 29 occasions subjects would be classified as reversible on FEV_1 criteria while a change beyond the immediate reproducibility of the IC test was seen on 27 occasions.

The bronchodilator drugs had a variable effect on resting tidal flow limitation. Figure 4 shows tidal flow-volume loops in the presence of NEP superimposed on the preceding loop in the absence of NEP in patient 3. In fig 4A subject 3 is non-flow limited before nebulised salbutamol but in fig 4B flow limitation has occurred after nebulised salbutamol. Despite this, expiratory flow increased significantly

Table 2 Mean (SE) changes in respiratory parameters after saline on two days and after salbutamol and ipratropium alone and in combination on each of the two days tested

	FEV_1 (l)	*FVC (l)*	*IC (l)*	*SVC (l)*	*FEV_1/FVC (%)*	*FEV_1/SVC (%)*
Saline (day 1)	0.02 (0.01)	0.02 (0.01)	0.00 (0.04)	−0.01 (0.07)	0.83 (1.15)	0.69 (0.52)
Saline (day 2)	0.01 (0.02)	0.01 (0.02)	0.07 (0.04)	0.16 (0.06)	0.36 (0.96)	0.92 (0.62)
Salbutamol	0.11 (0.02)*	0.33 (0.05)*	0.21 (0.05)*	0.35 (0.06)*	−0.66 (0.91)	0.82 (1.0)
Ipratropium	0.09 (0.02)*	0.34 (0.05)*	0.22 (0.04)*	0.35 (0.06)*	−0.69 (0.63)	−0.79 (1.0)
Combination (day 1)	0.16 (0.02)*	0.44 (0.07)*	0.34 (0.06)*	0.42 (0.08)*	−2.06 (2.13)	2.15 (1.3)
Combination (day 2)	0.15 (0.02)*	0.46 (0.07)*	0.34 (0.06)*	0.45 (0.08)*	−2.32 (1.97)	0.42 (1.08)

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IC = inspiratory capacity; SVC = slow vital capacity. Day 1 represents the day on which all subjects received salbutamol first, and day 2 is the day on which the first active drug given was ipratropium.
*p<0.001 compared with baseline.

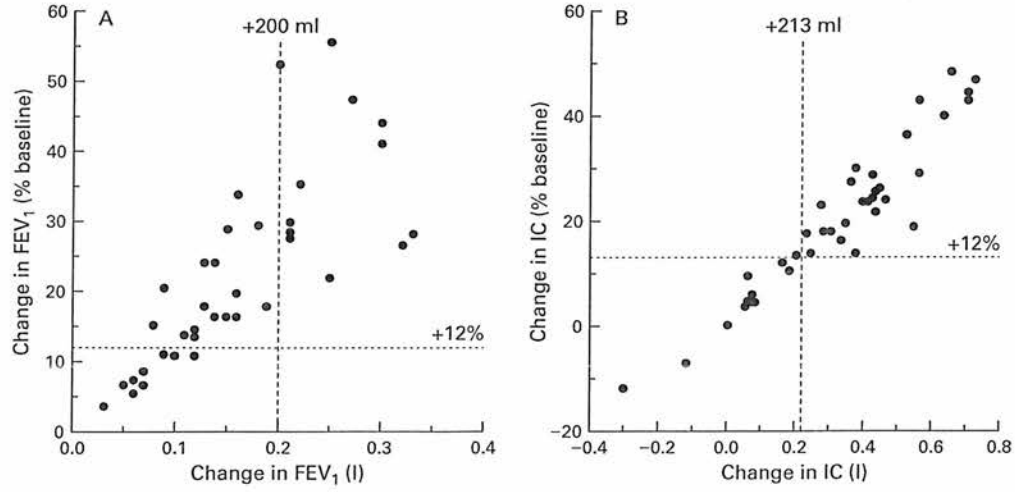

Figure 3 Changes in (A) forced expiratory volume in one second (FEV_1) and (B) inspiratory capacity (IC) after the combination bronchodilator on both days plotted as the absolute change against the change as a percentage of baseline value with each subject providing two data points, one for each day of testing (n=40). $r^2 = 0.648$ for FEV_1 and $r^2 = 0.905$ for IC. Two lines have been superimposed on these plots, representing a percentage change of 12% and an absolute change of 200 ml for FEV_1 and 213 ml for IC. The value of 213 ml represents the group mean increase in IC seen after saline (placebo) in our study. 200 ml and 12% are the values recommended by the ATS for satisfaction of FEV_1 reversibility criteria. Few subjects are irreversible using these criteria.

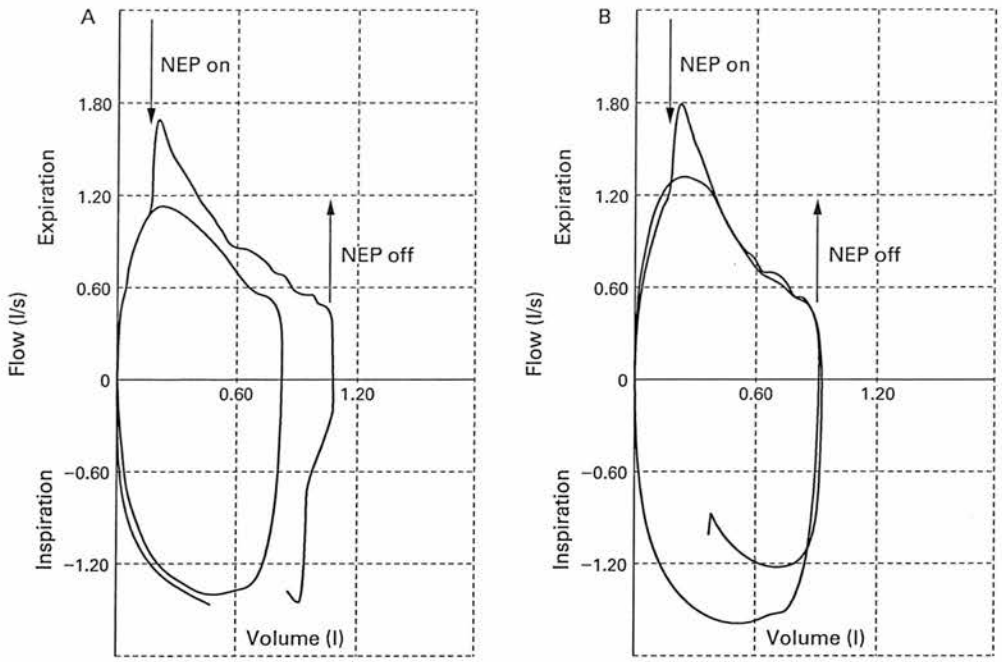

Figure 4 Negative expiratory pressure (NEP) traces of a typical subject (subject 3). Flow and volume are plotted against each other on the y and x axes respectively, both in the absence and the presence of NEP. The arrows denote the points at which NEP is applied and removed. (A) NEP trace after saline showing no flow limitation at any point during expiration. (B) NEP trace of the same subject after 5 mg nebulised salbutamol showing flow limitation throughout the whole of expiration. Despite the flow limitation there is a significant increase in the expiratory flow rate and in tidal volume from 0.79 to 0.89 litres.

after salbutamol. In nine individuals flow limitation was reduced after the single dose of bronchodilator and in seven after the combination of the two drugs. However, the number of individuals in whom this occurred was significantly different if the post saline data were used instead. Of the nine who became less flow limited after a single agent, seven became more flow limited after adding a second bronchodilator and two remained the same. None became less flow limited after the addition of a second agent. Post-bronchodilator NEP did not predict those who showed the greatest changes in FEV_1 or IC with bronchodilator drugs, alone or in combination.

The breathing pattern analysed at rest and the changes produced by the single and combination bronchodilator drugs are shown in table 3. Data for both the β agonists and anticholinergic drugs were combined as they showed no significant differences when analysed separately. There were no changes in the timing or frequency of respiration after any of the bronchodilator drugs, but there was a significant increase in the tidal volume representing a rise of 12.7% and 15.5% from the baseline breathing pattern after single and combination bronchodilator treatment, respectively. Mean inspiratory flow (Vt/Ti) did not change after the bronchodilators but mean expiratory flow (Vt/Te) showed significant improvements after each drug singly and in combination, but not after normal saline. When taken with the changes in EELV, the resultant changes in EILV were −0.24 (0.15) l and −0.41 (0.19) l after the single and combination bronchodilators, respectively. There were no significant differences in the measurements of inspiratory or expiratory muscle strength at any point during the testing, but there was a significant fall in mean (SE) perceived breathlessness from 3.4 (0.4) to 1.8 (0.3) after the combination treatment but not after treatment with a single agent ($p<0.05$). These changes in resting breathlessness were not correlated with those in IC, FEV_1, SVC, or any other volume based derivative.

Discussion

Bronchodilator reversibility testing is an important way of excluding a significant asthmatic component in patients with COPD but is relatively ineffective at predicting symptomatic benefit in severe disease.[5 6] Our data, together

Table 3 Mean (SE) changes in breathing pattern after placebo (saline), a single bronchodilator drug (either salbutamol or ipratropium but with data from both days combined, n=40)) and both drugs in combination

	Baseline	*Change after saline*	*Change after single drug*	*Change after combination*
Tidal volume (Vt) (l)	0.69 (0.02)	0.02 (0.02)	0.09 (0.02)*	0.11 (0.02)*
Respiratory frequency (/min)	24.4 (0.85)	−0.13 (0.39)	0.38 (0.51)	0.98 (0.58)
Inspiratory time (Ti) (s)	1.01 (0.04)	−0.01 (0.02)	0.02 (0.02)	0.03 (0.03)
Total respiratory time (Ttot) (s)	2.6 (0.09)	0.02 (0.04)	0.01 (0.05)	−0.06 (0.07)
Ti/Ttot	0.39 (0.01)	−0.01 (0)	0.01 (0)	0.41 (0.01)
Vt/Ti (l/s)	0.71 (0.03)	0.03 (0.01)	0.09 (0.02)	0.1 (0.03)
Vt/Te (l/s)	0.46 (0.02)	0.01 (0.01)	0.07 (0.01)*	0.10 (0.01)*

*$p<0.05$.

with those of others,[10 25] suggest that significant changes in IC and hence pulmonary hyperinflation occur after both β agonists and anticholinergic drugs. These changes were not accompanied by reproducible improvements in tidal airflow limitation nor did the presence of tidal flow limitation predict the changes in EELV or dyspnoea occurring after the bronchodilator. Changes in EELV were paralleled by those in SVC and FVC and were associated with improvements in tidal volume, which were larger when combination bronchodilator drugs were given. Unlike the NEP results, all volume related variables showed a continuous response to bronchodilators with no sign of a clear break between responders and non-responders. These data show that current physiological end points for reversibility testing are either insufficiently reproducible to give a reliable baseline value or are unable to identify "responder" subgroups, at least in patients with severe disease.

Our data have a number of strengths and limitations. Unlike previous studies we have included both a saline placebo comparison with our bronchodilator data and a randomised design. We used doses of bronchodilator high on the known dose-response relationships to ensure a maximum effect[26 27] and standardised the volume history and timing of all respiratory manoeuvres to diminish the effect of variation in the end expiratory pause on the expiratory flow rate.[28] Our findings are confined to patients with severe disease (<35% predicted FEV_1), partly because previous studies have shown more variable degrees of tidal flow limitation in patients with moderate disease[8] and also because we felt such patients will be the most likely to be "irreversible". We did not re-test our patients in the supine posture as we thought this likely to be impractical in clinical practice. Our measurements of flow and volume were very reproducible within individuals with a similar short term variability to that reported in severe COPD[7] and in patients with less marked airflow limitation.[29]

All of our patients had flow limitation when assessed conventionally using the maximum flow-volume envelope and without allowing for the effects of gas compression. We did not select them on the basis of pre-existing tidal flow limitation but because of the severity of FEV_1 assessed on normal spirometric tests. Like other studies,[8 9] we found that true tidal flow limitation was not present in most patients on NEP testing. However, despite the advantages of this type of assessment, we were disappointed to see that both the immediate and between day reproducibility of this measurement was inconsistent in patients of this severity studied in the seated position. This may reflect the fact that patients with more severe disease exhibit more dynamic regulation of their EELV than is the case in other subjects, even though there is no difference in baseline breathing pattern or IC on the different days. A variable effect of the small system dead space or the enhanced contribution of the abdominal muscles during quiet breathing may explain why, under some circumstances, the degree of tidal flow limitation varied. This has practical problems in terms of establishing a baseline for individual bronchodilator reversibility testing. In contrast, the measurements of lung volumes were more reproducible, those of FEV_1 being within the reported range for this measurement[7 13] while both SVC and FVC as well as IC measured from FRC were acceptable and consistent. The reproducibility of these volume based tests was equivalent to that of forced expiratory manoeuvres and broadly similar within individuals. Only when two inherently variable numbers (TLC and IC) were used to derive a third (EELV) did the variability become unacceptable. This problem has been noted previously when using derived lung volumes.[30]

The effects of the high dose nebulised bronchodilator drugs were very consistent. Although the drugs were given at different times and operate by different pharmacological mechanisms, there were no significant differences between the bronchodilator responses assessed by changes in IC or in any measure of expired volume after the β agonist or the anticholinergic agent. Post bronchodilator values were fivefold greater than the mean change seen after nebulised saline. As noted previously with inhaled ipratropium,[7] neither the FEV_1/FVC nor FEV_1/VC ratios were affected by high doses of nebulised bronchodilators, which suggests that the increase in FEV_1 resulted primarily from a fall in the operating lung volume. Addition of the second drug consistently produced further improvements in IC and lung emptying. The volumetric response was consistently greater than that after a single bronchodilator alone. Using the data derived from the short term reproducibility measurements, 29 of 40 measurements would be considered reversible on FEV_1 criteria and 27 on the basis of IC. However, these data do not show a definite threshold of response and, when examined over the 2 days of the study, all subjects showed an improvement in one or more variable after the combined bronchodilators. In contrast, the changes in tidal flow limitation given the variable baseline were very modest and in keeping with those reported by Tantucci *et al*[10] after a single smaller dose of inhaled salbutamol in patients with less severe COPD. The presence of complete tidal flow limitation did not preclude a relatively large change in EELV after the combination bronchodilator in these patients, which confirms that factors other than tidal flow limitation determine EELV in patients with advanced COPD. These data are the first to test directly the alternative hypothesis that a "poor response" to a bronchodilator is confined to patients without resting flow limitation[10 31] and, again, no clear pattern of response was seen.

Changes in the breathing pattern were not seen after nebulised saline but consistent improvements in tidal volume did occur after both anticholinergic and β agonist drugs. This initial increase in tidal volume amounted to approximately 50% of the change in EELV after the single bronchodilator, thereby reducing the change in EILV. Larger changes in tidal volume did not occur when the greater fall in

EELV was seen after the combination drugs and on this occasion EILV was also reduced. In keeping with the data of Belman *et al*,[6] it was at this point that the patients recorded a significant fall in the perceived level of resting breathlessness. The mean inspiratory flow (Vt/Ti), whether expressed as an absolute value or as a percentage of the vital capacity, was unchanged after the bronchodilator drug, suggesting that resting respiratory drive is well preserved in these individuals with resting tidal flow limitation or who are close to this state. However, we found consistent and highly significant improvements in mean expiratory flow after the bronchodilators, irrespective of the degree of tidal flow limitation. These data suggest that bronchodilators are acting to reduce the operating lung volume rather than resting inspiratory drive, in keeping with previous suggestions.[31] The changes in EELV after nebulised bronchodilators were of similar magnitude to those seen during exercise and to changes in resting EELV in less severe patients treated with salbutamol alone.[6] We believe that the improvements produced by the combination bronchodilators in our severe patients are likely to be translated into improved exercise performance.

The present data confirm the continuity of the bronchodilator response, however assessed, compared with placebo and this is seen even in patients who would be expected to have irreversible "flow limited" disease by conventional plethysmographic criteria. The separation of patients into "responders" and "non-responders" on the basis of short term spirometric changes is unlikely to be accurate whatever criteria or test is chosen. Despite the attractions of the NEP technique in objectively determining tidal flow limitation, it did not add further useful information when included as an outcome measure for bronchodilator testing, nor did it help to classify individuals who were likely to respond differently to treatment. In contrast, measurement of the IC was a useful guide as to when important changes in lung volume, associated with improvements in resting breathlessness, were likely to occur. It was as simple and reproducible as any of the other measures commonly reported. The improvements in EILV seen after a combination of high dose bronchodilators may explain why some individuals prefer wet nebuliser treatment to conventional metered dose inhalers[32] as significant improvements in IC occurred even when the change in FEV_1 would be considered barely significant. This technique may prove useful in assessing patients' suitability for home treatment with nebulised bronchodilators.

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Detection of expiratory flow limitation in COPD using the forced oscillation technique

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ABSTRACT: Expiratory flow limitation (EFL) during tidal breathing is a major determinant of dynamic hyperinflation and exercise limitation in chronic obstructive pulmonary disease (COPD). Current methods of detecting this are either invasive or unsuited to following changes breath-by-breath. It was hypothesised that tidal flow limitation would substantially reduce the total respiratory system reactance (Xrs) during expiration, and that this reduction could be used to reliably detect if EFL was present.

To test this, 5-Hz forced oscillations were applied at the mouth in seven healthy subjects and 15 COPD patients (mean±SD forced expiratory volume in one second was 36.8±11.5 % predicted) during quiet breathing. COPD breaths were analysed (n=206) and classified as flow-limited if flow decreased as alveolar pressure increased, indeterminate if flow decreased at constant alveolar pressure, or nonflow-limited.

Of these, 85 breaths were flow-limited, 80 were not and 41 were indeterminate. Among other indices, mean inspiratory minus mean expiratory Xrs ($\Delta\overline{Xrs}$) and minimum expiratory Xrs ($Xexp,min$) identified flow-limited breaths with 100% specificity and sensitivity using a threshold between 2.53–3.12 $cmH_2O \cdot s \cdot L^{-1}$ ($\Delta\overline{Xrs}$) and -7.38– -6.76 $cmH_2O \cdot s \cdot L^{-1}$ ($Xexp,min$) representing 6.0% and 3.9% of the total range of values respectively. No flow-limited breaths were seen in the normal subjects by either method.

Within-breath respiratory system reactance provides an accurate, reliable and noninvasive technique to detect expiratory flow limitation in patients with chronic obstructive pulmonary disease.

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Unlike healthy subjects who do not develop expiratory flow limitation (EFL) even during exhaustive exercise [1], many chronic obstructive pulmonary disease (COPD) patients are flow-limited (FL) at rest [2]. These patients can only increase their expiratory flow rate during exercise by allowing their end-expiratory lung volume (VL) to rise, an energetically inefficient strategy that is accompanied by severe dyspnoea that reduces exercise duration [3, 4]. The severity of dyspnoea in COPD is better predicted by the presence of EFL during tidal breathing than by the forced expiratory volume in one second (FEV1) [5, 6]. Thus, a simple method of detecting EFL during tidal breathing would be a potentially useful clinical tool. Several noninvasive methods have been proposed to detect tidal EFL in COPD patients, but each has its limitations and, to the best of the authors' knowledge, to date none has been tested against any form of "gold standard" in spontaneously breathing patients.

In 1993, PESLIN *et al.* [7] reported that some COPD patients during mechanical ventilation developed large negative swings in the respiratory system input reactance (Xrs, *i.e.* the imaginary part of total input impedance) measured by a forced oscillation technique (FOT). Similar behaviour was observed in a simplified mechanical model of the respiratory system when a flow-limiting segment was included [8] and in mechanically ventilated rabbits [9] after intravenous methacholine infusion. This phenomenon occurs because the linear velocity of gas passing through flow-limiting segments (choke points) equals the local speed of wave propagation [10]. Normally the reactance reflects the elastic and inertial properties of the respiratory system but when flow limitation is present, the oscillatory signal cannot pass through the choke points and reach the alveoli, producing a marked reduction in the apparent compliance (and, consequently, a fall in Xrs). These theoretical and experimental considerations make within-breath reactance measurement a potentially useful indicator of the occurrence of tidal EFL in COPD.

The authors hypothesised that the decrease of within-breath Xrs during expiration would allow the definition of a sensitive and specific method of determining the presence of EFL. To confirm this, breaths with and without a decrease in expiratory flow were studied while alveolar pressure (PA) increased, an independent way of identifying the presence of EFL in spontaneously breathing subjects.

Methods

Subjects

Fifteen stable COPD patients and seven age-matched healthy subjects were studied whose characteristics and lung

For editorial comments see page 187.

Table 1.–Physical characteristics and spirometric data of the subjects

Subjects	Age yrs	Weight kg	Height m	FEV1		FVC		FEV1/FVC	TLC		TGV		RV		Raw	
n				L	% pred	L	% pred		L	% pred	L	% pred	L	% pred	$cmH_2O \cdot s \cdot L^{-1}$	% pred
COPD 15																
Mean	72.5	68.2	1.70	1.0	36.8	2.2	61.1	47.6	7.9	123.1	6.1	174.6	5.3	204.3	7.3	325.7
SD	5.5	12.8	0.08	0.4	11.5	0.8	20.2	12.2	1.8	30.0	2.0	59.0	2.0	77.6	3.7	165.4
NFL 7																
Mean	72.7	65.3	1.70	1.2	43.4	2.7	75.4	45.0	8.8	134.7	7.0	196.3	5.8	221.7	5.7	255.2
SD	5.3	11.4	0.08	0.5	13.7	0.8	21.1	13.7	2.1	37.0	2.7	79.6	2.8	111.4	2.7	119.7
FL 6																
Mean	72.5	70.5	1.68	0.8	31.3	1.7	50.0	48.8	7.1	113.2	5.4	154.7	4.8	186.3	8.0	356.2
SD	6.8	16.4	0.09	0.3	5.3	0.4	7.6	12.7	0.9	21.5	0.8	28.8	0.7	29.6	4.6	207.2
Ind. 2																
Mean	72.0	71.5	1.68	0.8	30.0	1.5	44.5	53.0	7.1	112.5	5.5	158.5	5.1	197.5	10.0	446.0
SD	4.2	6.4	0.01	0.1	1.4	0.1	3.5	7.1	1.2	17.7	0.7	19.1	1.2	37.5	1.6	72.1
Healthy 7																
Mean	65.6	75.8	1.70	2.8	97.2	3.4	94.2	81.7	6.0	95.2	3.7	110.7	2.4	100.8	1.1	49.2
SD	10.3	8.3	0.01	0.6	18.9	0.7	17.9	4.3	0.9	15.0	0.9	30.3	0.9	37.5	0.8	35.3
p-value	NS	NS	NS	<0.001	<0.001	<0.005	<0.005	<0.001	<0.05	<0.05	<0.05	<0.05	<0.005	<0.01	<0.001	<0.001

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; TGV: thoracic gas volume; RV: residual volume; Raw: airway resistance; COPD: chronic obstructive pulmonary disease; FL: flow limited; NFL: nonflow limited; Ind: indeterminate; NS: nonsignificant. p-values are for COPD *versus* healthy subjects.

function are shown in table 1. The patients met the standard diagnostic criteria for COPD [11] and were current or exsmokers. They omitted their short- or long-acting bronchodilators for $\geqslant$3 and $\geqslant$12 h, respectively, before the study. Spirometry and subdivisions of VL were measured in a constant-volume body plethysmograph (Medgraphic Autolink 1085D, Medical Graphics, St Paul, MN, USA). Predicted values for flows and volumes were those recomended by the European Respiratory Society [12]. FOT was applied to the mouth of each subject while seated, wearing a noseclip and mouthpiece, during 2–3 min of spontaneous breathing. An operator firmly supported the cheeks to reduce upper airways shunt. The study was approved by the institutional research ethics committee, and written informed consent was given by each subject.

Measurements

Pressure (Pao) and flow (V'ao) at the airway opening were measured by a transducer (SCX01, SenSym, Milpitas, CA, USA) connected to the mouthpiece and by a screen-type pneumotachograph (4700A; Hans Rudolph, Kansas City, MO connected to a transducer LCVR, 0–2 cmH_2O; Celesco Instruments, Canoga Park, CA). Oesophageal pressure (Poes) was measured by a pressure transducer (SCX05, Sensym) connected to a standard balloon-catheter system placed in the lower oesophagus and filled with 0.4 mL of air. The position of the balloon was confirmed using the occlusion method [13]. All the signals were sampled at 200 Hz by an analogue-to-digital and digital-to-analogue board (DAQ-CARD 1200; National Instruments, Austin, TX) and recorded by a personal computer. The flow signal was integrated to give VL. The frequency response of the measuring systems [14] was flat up to 30 Hz.

Forced oscillations

The experimental set-up for FOT measurement is shown in figure 1. Healthy subjects and patients were studied while being oscillated by 5 Hz sinusoidal forcing with a pressure amplitude at the mouth of ~2 cmH_2O. The forcing frequency was chosen based on the preliminary model simulations presented in the Appendix. The same computer and board used to sample flow and pressure signals generated the forcing signal, which was amplified by a power amplifier (Proline EQ552; Eurosound, Milan, Italy) connected to a 25-cm diameter loudspeaker (HS250; Ciare, Ancona, Italy) mounted on a rigid box of ~2 L of internal volume. The pressure generated by the loudspeaker was transferred from the box through a connecting tube (22 cm in length, 19 mm in internal diameter) to the subject's mouthpiece. A low-resistance, high-inertance tube (35 mm in internal diameter and 1.5 m in length) in parallel with the loudspeaker allowed the subjects to breathe room air without significant loss of forcing pressure. A bias flow of ~15 $L \cdot min^{-1}$ reduced the equipment deadspace to the volume of the pneumotachograph and the mouthpiece [15].

Detection of expiratory flow limitation by the Mead and Whittenberger method

The method of MEAD and WHITTENBERGER [16] (M-W) of measuring pulmonary resistance was used to detect EFL during tidal breathing simultaneously with the application of forced oscillation. Briefly, the flow-resistive pressure (Pfr;

equal to P_{ao}–P_A) along the tracheobronchial tree was estimated by subtracting the elastic recoil pressure of the lung from transpulmonary pressure. During quiet breathing, elastic recoil pressure is directly proportional to volume. Thus a signal proportional to volume was subtracted from transpulmonary pressure. The constant of proportionality was adjusted so that the pressure at zero flow points at the beginning and end of inspiration were identical. Using zero-flow points to estimate P_{fr} the inertial pressure, even if very small during normal breathing, is neglected. Also lung tissue resistance, which may introduce a pressure drop between the pleura and the alveoli, and possible within-breath changes in upper airway resistance are neglected by the M-W method.

When the Lissajous figure in the P_{fr} *versus* flow graphs (fig. 2a–c) showed a loop where flow decreased during expiration while P_{fr} increased the breath was classified as "flow-limited" (FL; fig. 2c). Conversely, if the expiratory phase was characterised by a quasi-linear dependence between P_{fr} and flow with little or no loop the breath was classified as "nonflow-limited" (NFL; fig. 2b). In cases where it was not possible to be certain if flow limitation was present the breaths were classified as "indeterminate". This occurred in two different circumstances: when the inspiratory pressure/flow curve was looped instead of closed (possible errors in elastic recoil pressure estimation or an expiratory loop produced by the changes of V_L and not by EFL) or when the expiratory pressure flow curve was characterised by a clockwise loop in which flow decreased but P_{fr} did not simultaneously increase significantly.

Data analysis

Within-breath input impedance (Zin; and thus Xrs) was determined by using a least squares algorithm [17, 18] taking advantage of the *a priori* knowledge of the frequency spectrum components of the forcing signals. This method measures the input impedance for every acquired sample using a moving time window of pressure and flow signals of 0.2 s.

From the quiet breathing tracings, the longest period in which the breathing pattern was stable and without oesophageal spasms was selected. Four different indices based on the anticipated reactance change were used to detect EFL: 1) the mean value of Xrs during expiration ($\overline{X}$exp); 2) the minimal value of Xrs during expiration (Xexp,min); 3) the difference between the mean value of Xrs during inspiration ($\overline{X}$insp) and $\overline{X}$exp ($\Delta\overline{X}$rs); and 4) the difference between the maximal value of Xrs during inspiration (Xinsp,max) and Xexp,min (Xpeak-to-peak; fig. 3).

Different thresholds were applied to the values of each index ($\overline{X}$exp, Xexp,min, $\Delta\overline{X}$rs and Xpeak-to-peak) computed breath-by-breath. All breaths classified unequivocally by the M-W analysis as either FL or NFL were used to determine the sensitivity (the number of detected FL breaths divided by the total number of FL breaths) and specificity (the number of detected NFL breaths divided by the total number of NFL breaths) of each index. Sensitivity and specificity were calculated for the range of possible threshold values for each index in the following way: the total range of values assumed by an index was subdivided into 100 equally spaced points to provide a set of possible threshold values with good resolution. Then sensitivity and specificity were computed for each of the 100 values. These data were plotted as a function of the threshold value on the same graph. Areas where sensitivity and specificity curves were both 100% defined the optimal range of threshold values. Optimal threshold was chosen as the midpoint of this range.

Significance of differences of physical characteristics, spirometric data and Xrs indices' values between different groups was performed by a nonparametric (Mann-Whitney) test. Data are expressed as mean±SD unless otherwise stated.

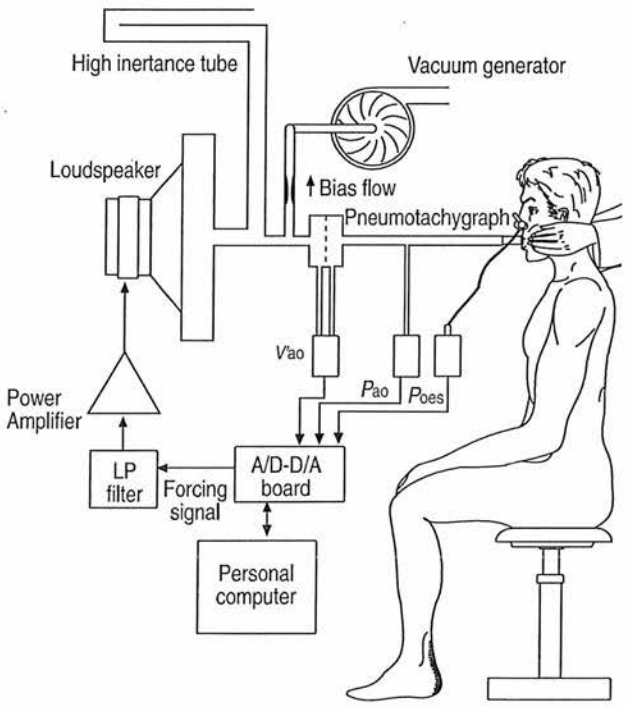

Fig. 1.–Experimental set-up for within-breath impedance measurement. V'_{ao}: flow at airway opening; P_{ao}: pressure at airway opening; P_{oes}: oesophageal pressure; LP: low pass; A/D-D/A: analogue-to-digital and digital-to-analogue.

Results

Representative Xrs data are presented in the lower panels of figure 2 where three experimental tracings of P_{fr} and Xrs obtained during a quiet breath are shown for a control, an NFL COPD patient and an FL COPD patient. The P_{fr} *versus* flow curve for the same breath is shown in the upper panel. Clear differences can be observed between the inspiratory and expiratory reactance in the patient where flow limitation was present (c and f) but not in the other examples.

In figure 3 the experimental tracings of volume, flow, pressure, total respiratory input resistance (Rrs) and Xrs are shown for a representative FL COPD patient. Note that the Rrs time course, unlike that for Xrs, did not present clear differences between inspiration and expiration. The within-breath fluctuations of Rrs were usually wider if EFL was present than in the absence of flow limitation, a finding common to most of the breaths studied. These results are in agreement with the model data presented in the Appendix. Of the 284 breaths (206 from patients and 78 from controls) selected, 12 breaths (4%) were discarded because of oesophageal spasms, spikes in the impedance due to glottis closure or swallowing, or because they showed an abnormal looping of the pressure/flow curve. The authors used 85 breaths classified unequivocally by M-W analysis as FL and 80 as NFL to determine sensitivity and specificity of the indices. Sensitivity and specificity plots are presented as function of the threshold value for each index (fig. 4). All indices had a region where both specificity and sensitivity were 100% but these regions

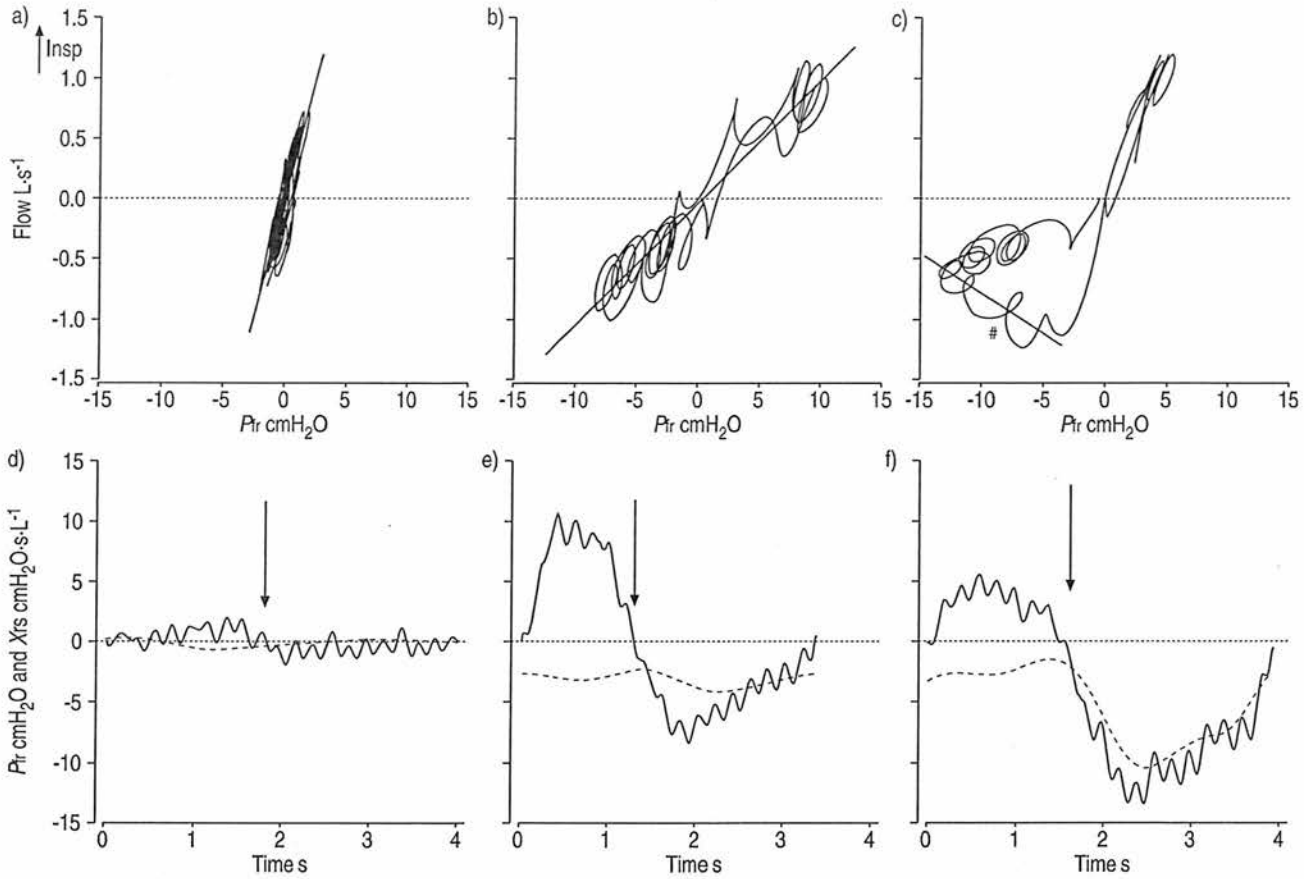

Fig. 2.–The Mead and Whittenberger graphs (a–c) obtained by plotting the airway opening flow *versus* the resistive pressure drop (P_{fr}) during a single breath. Data from a healthy subject (a and d), a nonflow-limited patient (b and e) and a flow-limited chronic obstructive pulmonary disease patient (c and f) are shown. The regression lines in a) (m=0.398, R=I/m=2.51 $cmH_2O \cdot s \cdot L^{-1}$) and b) (m=0.102, R=I/m=9.8 $cmH_2O \cdot s \cdot L^{-1}$) represent airway resistance at breathing frequency, m being the slope of the regression (airway conductance). In c), expiratory flow limitation ($^{\#}$) is demonstrated by the presence of a region in which airway opening flow is decreasing while P_{fr} is increasing. The lower graphs (d–f) show the corresponding time courses of P_{fr} (——) and respiratory system reactance (- - -). The arrows indicate the end of inspiration *i.e.* time before this point is inspiration and after is expiration.

had different widths. Total range, optimal range (range of threshold values in which both specificity and sensitivity were 100%), its percentage of the total range (optimal region) and the midpoint of the optimal range (optimal threshold) are shown in table 2 for each index.

The patients were then divided into three groups depending on the classification of their breaths analysed by the M-W. In 11 patients, all of the breaths were within the same classification, but in four patients different breaths were classified in different categories. However, in these patients there was always a clear majority of breaths (75% minimum) in the same category. Thus, six patients were classified as FL during tidal ventilation, seven patients as NFL and two patients as indeterminate.

In general, patients with more severe COPD were more likely to be FL, as would be expected. However, even if the FL patients presented in average a lower value of FEV1 than NFL (see table 1), the lowest FEV1 showed by NFL patients (25% predicted) was much smaller than the highest presented by FL patients (41% pred).

Mean values of all the indices for each patient and control subject are presented in figure 5 as well as the average values for each group. As expected there was a clear distinction between the FL and NFL groups with the two indeterminate patients presenting values similar to the FL patients. Healthy subjects presented values closer (even if statistically different) to NFL COPD patients.

The application of the threshold values determined in COPD patients to the indices computed for the healthy subjects indicates that in healthy subjects EFL was never present during quiet breathing, with values for all the indices clearly separated from the optimal threshold (horizontal dashed line in figure 5) selected from table 2.

Discussion

The ability to detect EFL reliably and noninvasively during tidal breathing is of both theoretical and practical value in patients with COPD. Current techniques all have significant disadvantages, although more recently developed methods based on detecting changes in expiratory flow when the driving pressure is increased are more convenient and simpler to apply than previous approaches [19, 20]. However, even these methods are limited in the number of breaths that can be tested and/or by the need to perform a specific respiratory manoeuvre. Moreover, none has been compared with an independent method to detect EFL during awake spontaneous breathing subjects

By definition, flow limitation occurs when maximum

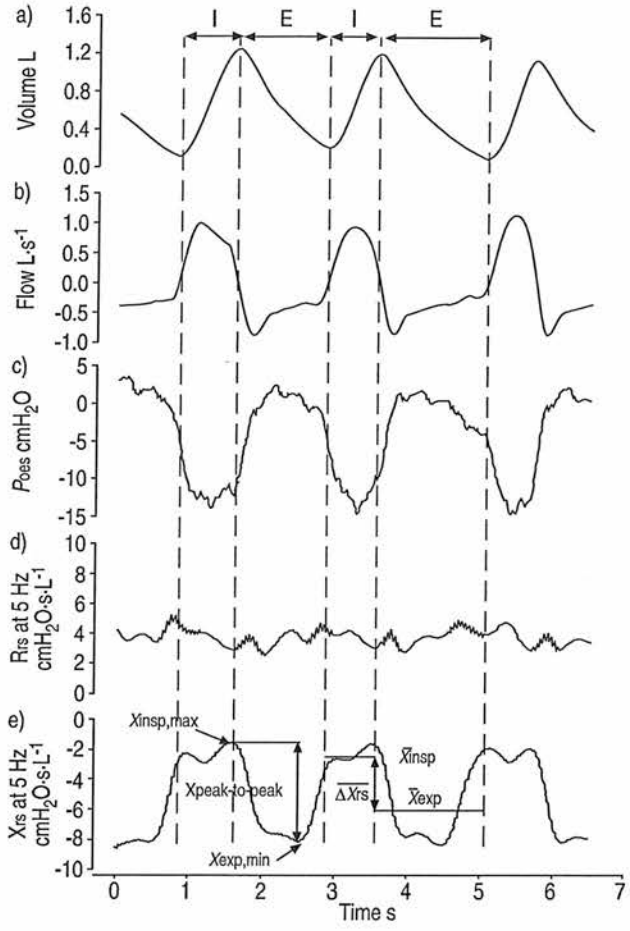

Fig. 3.–Experimental tracing from a representative flow-limited patient and definition of the indices used to characterise the respiratory system reactance (Xrs) time course during a single breath. a) Respiratory volume, b) flow at the airway opening, c) oesophageal pressure, d) total respiratory input resistance (Rrs) and d) Xrs at 5 Hz. $\overline{X}$insp: mean value of Xrs during inspiration; $\overline{X}$exp: mean value of Xrs during expiration; Xexp,min: minimum value of Xrs during expiration; Xinsp,max: maximum value of Xrs during inspiration. Since reactance was expected to decrease during expiratory flow limitation, the difference between $\overline{X}$insp and $\overline{X}$exp ($\Delta\overline{X}$rs) and the difference between Xinsp,max and Xexp,min (Xpeak-to-peak) was considered. Indices were defined in two different breaths for clarity. I: inspiration; E: expiration; Poes: oesophageal pressure.

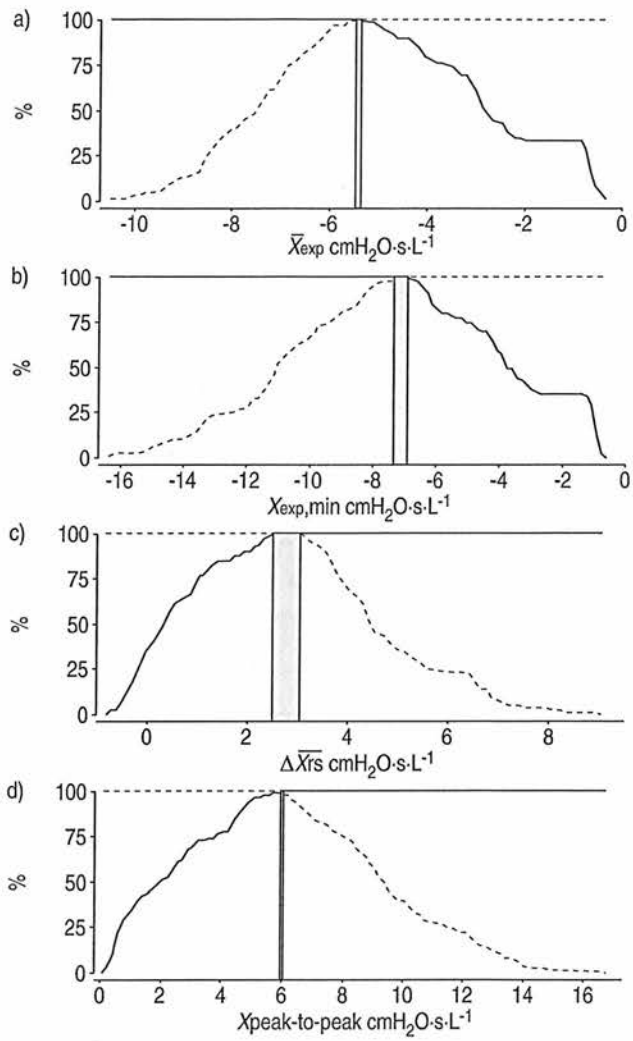

Fig. 4.–Sensitivity (- - -) and specificity (——) expressed as percentage of all the classifiable breaths (80 nonflow-limited and 85 flow-limited) are plotted *versus* the threshold values for the four considered indices. a) Mean expiratory Xrs value ($\overline{X}$exp), b) minimum expiratory Xrs value (Xexp,min), c) the difference between mean inspiratory and mean expiratory Xrs ($\Delta\overline{X}$rs) and d) the difference between maximum inspiratory and minimum expiratory Xrs (Xpeak-to-peak) were considered. The shaded bars represent the optimal region in which sensitivity and specificity are both 100%.

expiratory flow is reached on the plateau of the isovolume pressure/flow curves [21]. Unfortunately this approach is not suitable for a simultaneous comparison with the measurement of Xrs. Therefore, flow limitation was defined as a decrease in V'ao with an increase in *P*fr. This is essentially the same definition used in the negative expiratory pressure (NEP) technique; when a negative pressure is applied to the airway

Table 2.–Total range, optimal range, region width and threshold for respiratory system reactance (Xrs) indices in patients

Index	Total range cmH2O·s·L-1	Optimal range cmH2O·s·L-1	Optimal region %	Optimal threshold cmH2O·s·L-1
$\overline{X}$exp	-10.5– -0.3	-5.48 –-5.38	1.0	-5.4
Xexp,min	-16.4– -0.6	-7.38 – -6.76	3.9	-7.1
$\Delta\overline{X}$rs	-0.8–9.0	2.53–3.12	6.0	2.8
Xpeak-to-peak	0.1–16.7	5.99–6.02	0.2	6.0

$\overline{X}$exp: mean value of Xrs during expiration; Xexp,min: minimum value of Xrs during expiration; $\Delta\overline{X}$rs: the difference between $\overline{X}$insp and $\overline{X}$exp; Xpeak-to-peak: the difference between Xinsp,max and Xexp,min. Total range of values assumed by indices, optimal range (range of threshold values in which both specificity and sensitivity were 100%), its percentage of the total range (optimal region) and the midpoint of the optimal range (optimal threshold) are reported. Indices are as described in the text.

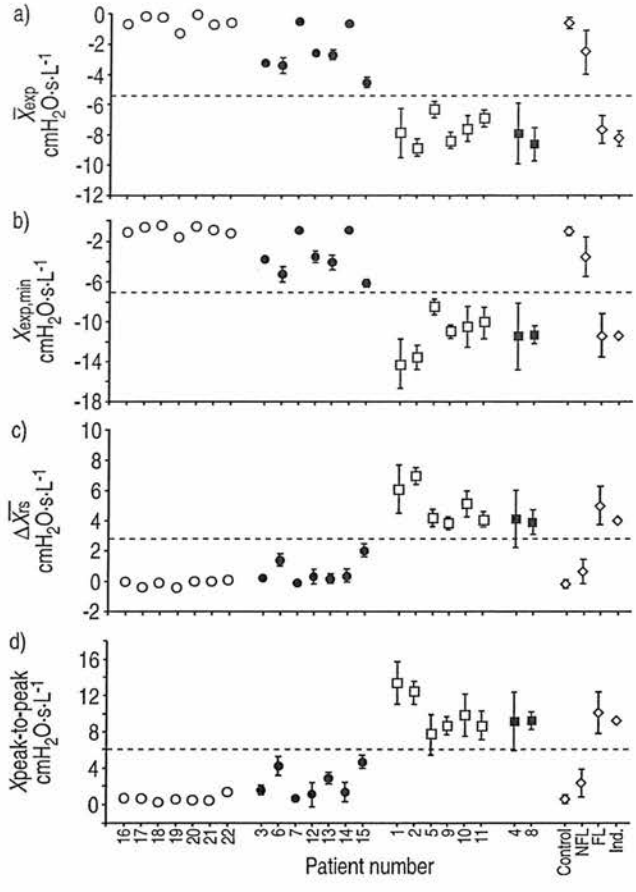

Fig. 5. – Mean±SD values of the considered indices computed on all the breaths from a given subject are shown. Control subjects (○), nonflow-limited (NFL; ●), flow-limited (FL; □) and indeterminate (Ind.) chronic obstructive pulmonary disease patients (■) and mean±SD of each group (◇). a) Mean expiratory respiratory system reactance (X_{rs}) value, b) minimum expiratory X_{rs} value, c) the difference between mean inspiratory and mean expiratory X_{rs} ($\Delta\overline{X_{rs}}$) and d) the difference between maximum inspiratory and minimum expiratory X_{rs} ($X_{peak\text{-}to\text{-}peak}$) were considered. In all the graphs, the optimal threshold value (table 2) is plotted as a horizontal dashed line.

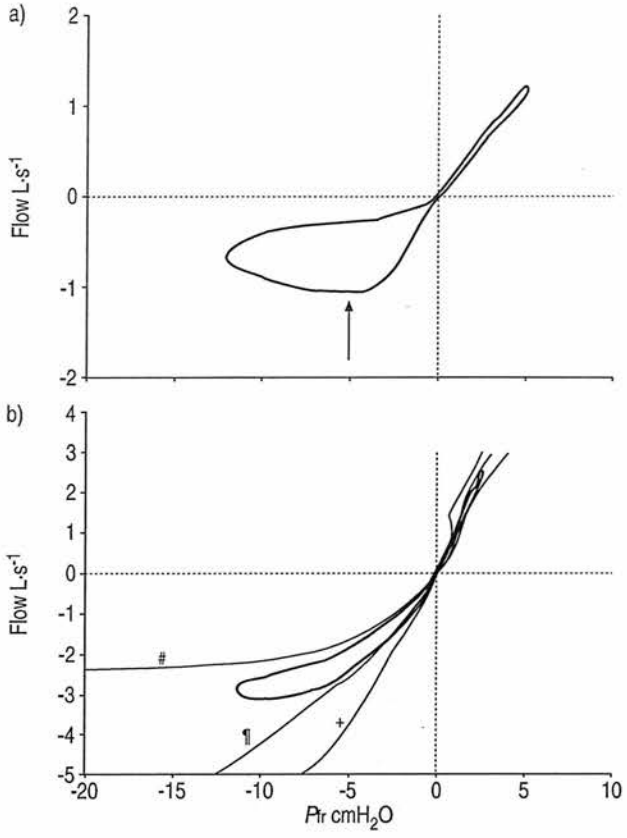

Fig. 6. – Schematic of a) flow-resistive pressure drop (P_{fr}) *versus* flow diagram in presence of flow-limitation and b) in case of dynamic compression of airways combined with volume dependence of resistance in the absence of choke points. In a) the arrow indicates the onset of expiratory flow limitation. In b) there are three schematic isovolume pressure/flow curves (thin lines) at 25% (#), 50% (¶) and 75% (+) vital capacity (VC). On the same plot a schematic pressure/flow loop during a tidal breath is also shown (thick line). This last plot takes into account the increase in resistance as lung volume decreases. Thus, if the expiration starts for instance at 50% of VC, the quiet-breathing (QB) loop at the beginning will be very close to the isovolume pressure/flow curve at 50% VC. Then the lung volume will decrease, leading to the separation of the QB loop from the 50% VC isovolume curve and then approaches, for instance, the 25% isovolume curve at the end of expiration. The schematic was drawn by hand and the values of 50 and 25% of VC for end inspiration and end expiration are arbitrary and considered only for clarity.

opening, thereby increasing P_{fr}, flow limitation is assumed to be present if expiratory flow does not increase. However, NEP was not used as a gold standard, as its assumptions have never been validated by comparison with other physiological measurements of EFL in spontaneously breathing unsedated patients. Instead the M-W technique was used; when P_{fr} increases and flow decreases, there is a clockwise loop in the expiratory P_{fr}/V'_{ao} curve that is not seen during inspiration (fig. 6a). This method of detecting EFL in each breath has a number of advantages. It is independent of upper airway compliance that can potentially influence the results of NEP measurements. Like NEP it is not influenced by the previous V_L history as it does not require specific respiratory maneuvers to be performed. However, it is recognised that it is possible for such a loop to be present when dynamic compression of airways is combined with volume dependence of resistance in the absence of choke points, completely limiting expiratory flow as illustrated in the schematic shown in figure 6b. In this situation, X_{rs} would not decrease when, according to the M-W criterion (and NEP), there was EFL. Alternatively, choke points could develop in some parallel pathways before expiratory flow was completely limited. If this were to occur, the authors predict that the forced oscillations would penetrate to those alveoli where flow was not yet limited, but would not pass through the choke points that were established in parallel. This would cause a fall in X_{rs}, but not to the extent as would occur when choke points limited all expiratory flow, while NEP should indicate lack of flow limitation.

Ideally, the authors would have preferred a gold standard methodology that only detected complete EFL produced by choke points. In practice, the comparator used encompassed the possibility of no flow limitation with volume dependence of resistance combined with early dynamic compression of airways insufficient to limit flow and also of partial EFL by choke points in some parallel pathways but not in others. Measurement of X_{rs} is likely to be insensitive to the volume-dependent effects, sensitive to complete EFL and intermediate with partial EFL. A false-positive M-W analysis due to early dynamic compression and volume dependence of resistance

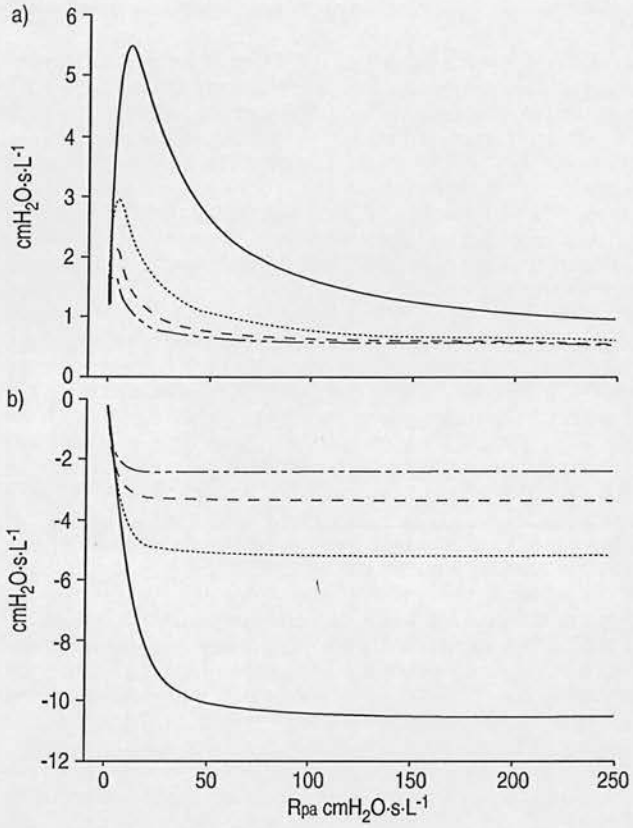

Fig. 7.–Simulated a) real and b) imaginary part of the input impedance at 5 (—), 10 (·····), 15 (- - -) and 20 (–·–·) Hz of a lumped parameter model of the respiratory system that includes airway wall shunting. Real and imaginary parts are plotted *versus* peripheral airway resistance (R_{pa}) that is increased to simulate the occurrence of expiratory flow limitation. See Appendix 1 for details.

would appear as a lack of sensitivity of Xrs indices to detect EFL. As this was never seen over the optimal range of threshold values (table 2 and fig. 4), false-positive results with this method are probably rare.

If partial flow limitation had caused a false-positive M-W analysis that was also detected by Xrs analysis, the sensitivity curves in figure 4 would have reached 100% earlier, leading to a large optimal range. The fact that these ranges were small for X_{exp} and $X_{peak\text{-}to\text{-}peak}$ argues against this being a significant problem. If Xrs analysis were insensitive to partial EFL it would again reduce the test sensitivity, which was not the case.

The transition from NFL expiration to complete EFL has not been carefully studied. Sophisticated modelling combined with careful physiological measurements during this transition are needed to clarify this issue. The forced oscillation method can help by giving a quantitative estimate of the degree of EFL. Xrs should fall as each new choke point develops by an amount dependent on the elastic properties of that part of the tracheobronchial tree subtended by the airway in which the choke point occurs. However, the degree of Xrs reduction during EFL also depends on the mechanical properties of airway walls (which may be hypercompliant in COPD [22]) and on the location of the choke points. Nevertheless, in this study, the intrasubject variability of airway wall properties or location of choke points did not prevent the definition of a single threshold value (independent from subject characteristics) that reliably indicates the presence or absence of EFL.

In this study, the authors have developed indices from Xrs measurements that detect EFL robustly. From these indices they were able to identify threshold values, obtained in a limited number of patients, between which sensitivity and specificity were 100%. In a larger patient population it is possible that these thresholds may change somewhat. This clear separation of values also precluded the use of receiver operator characteristic analysis.

Although all the indices detected EFL, each had advantages and disadvantages. $\Delta\overline{Xrs}$ presented the clearest separation between FL and NFL breaths in the sensitivity-specificity plots (fig. 4). Moreover, this index is less dependent on baseline airway mechanics being based on a relative change rather than an absolute value. Indices based on mean values are more robust because they are less affected by signal noise, but must be computed using the whole breath. The index based on the minimum expiratory Xrs is well suited to study changes in flow limitation during the breath; the point when the actual Xrs value falls below the threshold indicates the onset of flow limitation that persists until Xrs returns to values higher than threshold. This index could be used to detect the $V\!L$ at which EFL occurred (and thus to automatically compute, for instance, the percentage of a tidal breath that is FL) and the relative value of the limiting flow.

In all the analyses the Xrs data was expressed as the absolute values and the relative changes of reactance rather than expressing data as a percentage of baseline (*i.e.* inspiratory Xrs) [9], since the inspiratory Xrs values can range from slightly positive to negative depending on the mechanical properties of the respiratory system of the subject. However, the use of physical units should not prevent the application of the Xrs thresholds to new patients and data sets. In fact, whatever the condition of the patient, the difference between the impedance of the shunt pathway due to airway wall compliance (measured by expiratory Xrs if EFL is present) and the open lung (measured by Xrs during inspiration) is so high (approximately one order of magnitude) that even differences on airway wall mechanical properties due to intersubject variability or to the disease should only marginally affect the changes in Xrs during expiration. Moreover, as shown in the Appendix and in figure 7, Xrs is very sensitive to the increase of peripheral airways resistance only at the beginning and rapidly reaches a plateau. These observations suggest that the thresholds should only marginally be affected by changes in lung and airways mechanics. This is also supported by the 100% sensitivity and specificity obtained studying a very heterogeneous patient population (table 1). Finally, even if the oscillatory pressure applied to the subject during FOT was very small (<2 cmH_2O) and with a zero mean value (as it was a sinusoidal forcing), it is possible that the dead space and the resistance added by the device may have induced changes in patients' $V\!L$ and breathing pattern. As a result, the condition of the patients during the measurements may have been different from baseline spontaneous breathing. However, the amount of dead space and resistance of the device was similar to any measurement system that uses pneumotachographs (as NEP or spirometers). Therefore, the effect of FOT on breathing pattern is likely comparable with any other EFL monitoring system.

Since changes in Xrs can be due to either EFL or airway closure, it is possible that the swing in Xrs may be due in part to the latter phenomenon, affecting the reliability of the technique to selectively detect EFL. However, as shown in figure 3, the time course of Xrs is not in phase with volume. Typically, Xrs should increase from mid- to late expiration, and at end-expiration is close to its value at end-inspiration. This is the expected pattern if Xrs is detecting flow limitation, which does not persist to the end of expiration but stops before expiratory flow does when pleural pressure falls and

the airways are no longer dynamically compressed. If airway closure were occurring, it should increase throughout expiration and Xrs would continue to fall until end-expiration and remain low throughout early inspiration before all closed airway reopened. This behaviour was not observed, since Xrs starts to return to pre-expiratory values before end-expiration. This happens as *P*oes begins to fall (see fig. 3).

The fall in *P*oes due to pre-inspiratory inspiratory muscle recruitment necessary to overcome intrinsic positive end-expiratory pressure can decrease dynamic compression so that flow limitation is no longer present. It cannot, however, open airways closed below closing volume as long as $\dot{V}L$ is still decreasing. Reopening of closed airways below closing volume only occurs after inspiratory flow starts and $\dot{V}L$ reaches opening volume. Thus, the increase in Xrs toward the end of expiration must be due to either partial or complete reopening of choke points.

However, a perfect quantification of flow limitation and airway closure contributions to Xrs is very difficult in these circumstances. Nevertheless it is important to underline that it is impossible to differentiate the impact of airway closure and EFL during an expiration using any noninvasive monitoring approaches (including NEP).

These data are in keeping with the theoretical basis for using the negative swing in Xrs to detect EFL. The Xrs value at a given frequency results from two opposite contributions: one negative, related to compliance and one positive related to inertance. Thus, the observed within-breath changes in Xrs can be due to either a reduction in the apparent compliance and/or a decrease of inertance. Lung and chest wall compliances are functions of volume and not flow, and in the absence of airway closure in expiration and reopening in inspiration or the development of choke points during expiration they should change very little during the respiratory cycle. Inhomogeneities of the time constant can lead to lower values of Xrs in COPD compared with healthy controls (as in fig. 2), but, unless airway closure is occurring, inhomogeneities can only contribute for a small fraction of the changes of Xrs observed in the presence of EFL [23], even if they decrease substantially during inspiration, as a result of the dilatation of the peripheral airways. Respiratory system inertance is mainly due to gas acceleration in the airways [24] and the mass of the abdomen. At 5 Hz its contribution to total Xrs is in the order of 0.4 $cmH_2O \cdot s \cdot L^{-1}$ [25]. The mean within-breath peak-to-peak difference of Xrs observed in the FL patients was 10.31 $cmH_2O \cdot s \cdot L^{-1}$ (fig. 5d), therefore even the maximum possible decrease of inertance to zero can account for only a negligible part (~5%) of the observed reduction. Thus changes of inertance are unlikely to play a significant role in the changes in Xrs that were measured.

In summary, these data indicate that the measurement of expiratory reactance during tidal breathing can reliably detect breaths that are flow-limited and potentially the time at which flow limitation begins. A further useful feature of this method is its ability to identify periods in which total respiratory input resistance no longer reflects the mechanical properties of the respiratory system due to the presence of expiratory flow limitation. This technique is simple to use, sensitive, specific and noninvasive. The ability to analyse multiple breaths in different circumstances makes this a useful method in conditions where flow limitation has been hard to measure, such as during exercise and in the intensive care unit. Moreover, this noninvasive technique is particularly suited to evaluating clinical interventions such as bronchodilator treatment where it will allow the monitoring of more relevant variables than the forced expiratory volume in one second, and potentially identify those patients who benefit most from therapy.

Appendix

To evaluate the impact of the different forcing frequencies on the Xrs swings observed when passing from FL to NFL conditions the authors modelled the respiratory system as a simple lumped parameter model derived from the two-compartment model proposed by MEAD [26]. The model considers the airways to be compliant structures that may shunt some of the forced oscillatory flow. The present model consisted of an airways compartment in series with parallel alveolar gas compliance and lung-chest wall tissue compartments.

Airways were modelled as an upper airway resistance (0.5 $cmH_2O \cdot s \cdot L^{-1}$), an airway inertance (0.002 $cmH_2O \cdot s^2 \cdot L^{-1}$), an airway wall compliance (0.002 $L \cdot cmH_2O^{-1}$) shunt pathway and a peripheral airway resistance (Rpa) connected as a T network. The airways compartment (on the Rpa side) leads to a gas compression compliance (equivalent of 3L of air) in parallel with the tissues, modelled as a resistance (Rt; 0.5 $cmH_2O \cdot s \cdot L^{-1}$) in series with a compliance (CL,dyn; 0.05 $L \cdot cmH_2O^{-1}$) [25]. Using this simple model, the authors simulated the effect of the onset of EFL as the increase of Rpa from a baseline value of 0.5 up to 250 $cmH_2O \cdot s \cdot L^{-1}$ [27].

In figure 7, the real and the imaginary part of the Zin presented by the model are expressed as a function of Rpa. As soon as Rpa increases the shunt pathway due to the airway walls compliance affects the total input impedance by reducing Xrs. Even when this reduction is present at all the frequencies, the greatest difference is seen at the lowest frequency. Therefore, to obtain larger Xrs swings from inspiration to expiration when expiration is flow-limited (and thus increasing the sensitivity of the indices), the lowest possible frequency was chosen. Since the quiet breathing signal can interfere with the estimation of Zin at frequencies below 5 Hz, 5 Hz was used as forcing frequency in this study. This forcing frequency allows for a time resolution of 0.2 s (*i.e.* one period of the forcing signal).

Figure 7 also shows that the real part of Zin is not monotonic, with an increase at the beginning followed by a decrease. This suggests that Rrs is not suitable for the detection of EFL as the same value of Rrs can be measured in presence of both a mild or a massive increase in Rpa.

This model is an extremely simplified representation of the respiratory system that considers only one pathway (instead of several heterogeneous airways) with constant values for the several parameters instead of considering possible within-breath variations. The authors accept that the transition phase between non-EFL to EFL during an expiration is a complex and heterogeneous phenomenon, both in time and in the location and the number of pathways involved; therefore its use is rather speculative. Nevertheless, it was found that the Xrs values measured at different frequencies (5, 11 and 19 Hz) during EFL in a subset of the COPD patients frequency are well represented by this model, when Rpa assumes very high values.

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Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD

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ABSTRACT: Bronchodilator drugs produce variable improvements in forced expiratory volume in 1 s (FEV_1), but larger changes in end-expiratory lung volume (EELV) in chronic obstructive pulmonary disease (COPD), which were suggested to be related to the presence of expiratory flow limitation (EFL) at rest.

We tested this concept in 42 COPD patients (FEV_1 42.3±13.8% predicted) during spontaneous breathing before and after 5 mg nebulised salbutamol. EFL was detected by within-breath changes in respiratory system reactance measured by a multifrequency forced oscillation method, while changes in EELV were assessed by inspiratory capacity (IC). Bronchodilation (BD) increased IC (from 1.8±0.5 to 2.1±0.6 L, $p<0.001$) and reduced inspiration resistance ($\bar{R}_{insp}$) at 5 Hz (from 5.1±1.6 to 4.2±1.5 $cmH_2O \cdot s \cdot L^{-1}$, $p<0.001$). $\bar{R}_{insp}$ identified BD responders with a discriminative power of 80.1%.

In total, 20 patients were flow-limited before BD. They showed worse spirometry and higher residual volume, but significant improvements in IC were seen in all patients irrespective of flow limitation. Changes in $\bar{R}_{insp}$ were confined to flow-limited patients, as were reactance changes. BD reduced the degree of heterogeneity in the respiratory system, a change best seen with inspiratory values.

BD has complex effects on lung mechanics in COPD, and EFL affects both this and the response of some respiratory variables to treatment. However, changes in EELV are consistently seen, irrespective of the presence of flow limitation at rest.

KEYWORDS: Chronic obstructive pulmonary disease, forced oscillation technique, respiratory system reactance, within-breath impedance

Chronic obstructive pulmonary disease (COPD) is defined by the presence of incompletely reversible expiratory airflow limitation (EFL) [1], which occurs at much lower flows for any given lung volume when compared with healthy subjects. Initially, flow limitation is only present during maximal or near maximal respiratory efforts, but as lung disease progresses, EFL develops at rest in many, but not all, individuals [2]. The presence of resting EFL may identify COPD patients who behave differently and who develop dynamic hyperinflation [3], at least during exercise [4].

Bronchodilator drugs improve lung emptying, and this leads to variable increases in forced expiratory volume in 1 s (FEV_1), mainly by reducing lung volume rather than changing the FEV_1/forced vital capacity (FVC) ratio [5]. However, the reproducibility and predictive value of testing for FEV_1 reversibility is relatively poor [6, 7], while the change in resting inspiratory capacity has been shown to be a better predictor of improvement in exercise performance [8, 9]. Again, patients with EFL have been reported to show improvements in inspiratory capacity after bronchodilators [10], which may relate to an improvement in exercise performance [11].

Previous workers have used the negative expiratory pressure method to detect EFL [12], but that study samples a relatively small number of breaths and not all tests are suitable for analysis [2]. We

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have developed an effort-independent method to determine flow limitation during tidal breathing using the forced oscillatory technique to identify within-breath differences in respiratory system reactance [13, 14]. This method allows the assessment of more breaths, is equivalent to the negative expiratory pressure approach when both can be recorded [2], and adds a potential "quantitative" assessment of how close the patent is to the threshold of EFL [14]. Modelling simulations based on these data suggest that EFL will influence other measurements of oscillatory mechanics during expiration, and this will reduce the sensitivity of expiratory impedance data to change after interventions, such as bronchodilators. Although this effect can be identified when within-breath analysis is performed [13], most published reports of oscillatory mechanics in COPD only report total respiratory cycle data [15–17].

In the current study, we tested the hypothesis that the changes in lung volume (specifically inspiratory capacity) and oscillatory lung mechanics of COPD patients given an inhaled bronchodilator drug would differ when EFL was present, and whether this would be unrelated to the presence of reversibility defined spirometrically. Additionally, we extended our observations of within-breath impedance using a forced oscillation method from single to multiple forcing frequencies. This approach allowed us to test whether bronchodilator drugs improve resistance and the intrapulmonary homogeneity of lung mechanics, avoiding the confounding effects of EFL on impedance data that would be corrupted when adopting the conventional multifrequency approach. Finally, we examined the changes in resting lung and respiratory system mechanics in those individuals who were no longer flow-limited after the bronchodilator drug.

METHODS

Subjects

We recruited clinically stable outpatients who met the diagnostic criteria for COPD [18] and were either current or ex-smokers. All patients were using short- and long-acting inhaled bronchodilators, which were omitted before study for 3–24 h, as appropriate. The study was approved by the institutional research ethical review committee (South Sefton Research Ethics Committee, Liverpool, UK), and written informed consent was given by each subject.

Measurements

Forced expiratory flow, lung volume and subdivisions were measured by a constant-volume body plethysmograph (Medgraphic Autolink 1085D; Medical Graphics, St Paul, MN, USA). All measurements met current standards for acceptable data quality [19]. We report FEV_1, FVC, FEV_1/FVC, inspiratory capacity (IC), residual volume (RV), thoracic gas volume (TGV) and total lung capacity (TLC) both as absolute values and % predicted (% pred). Predicted values were those recommended by the European Respiratory Society (ERS) [20].

We measured breathing pattern and oscillatory mechanics using previously described methods [13]. Briefly, we recorded pressure and flow at the airway opening by a transducer connected to the mouthpiece (PXLA0025DN; Sensym, Milpitas, CA, USA) and by a screen-type pneumotachograph (3700A, Hans Rudolph, Kansas City, MO, USA) connected to another pressure transducer (PXLA02X5DN, 0–2.5 cm; Sensym). All the signals were sampled at 200 Hz and recorded onto a PC. The flow signal was integrated to give lung volume, and volume drift was removed by selecting 2–3 min of stable quiet breathing and estimating the linear trend on the integrated signal. This trend was then removed from the traces.

From these signals we measured tidal volume (V_T), respiratory frequency, total cycle duration, inspiratory time, expiratory time and inspiratory duty cycle (fig. 1). We derived minute ventilation (V'_E), mean inspiratory flow rate and mean expiratory flow rate from these data.

Forced oscillations

Patients were studied while being oscillated by the following two different waveforms: 1) a 5 Hz sinusoidal signal, and 2) a pseudo-random noise (PRN) with three components at 5, 11 and 19 Hz chosen to be non-sum non-difference of order 3 [21]. For both the waveforms, the peak-to-peak pressure amplitude measured at the mouth was ~1–2 cmH_2O. In order to have comparable total energy at 5 Hz in both the sinusoidal and the

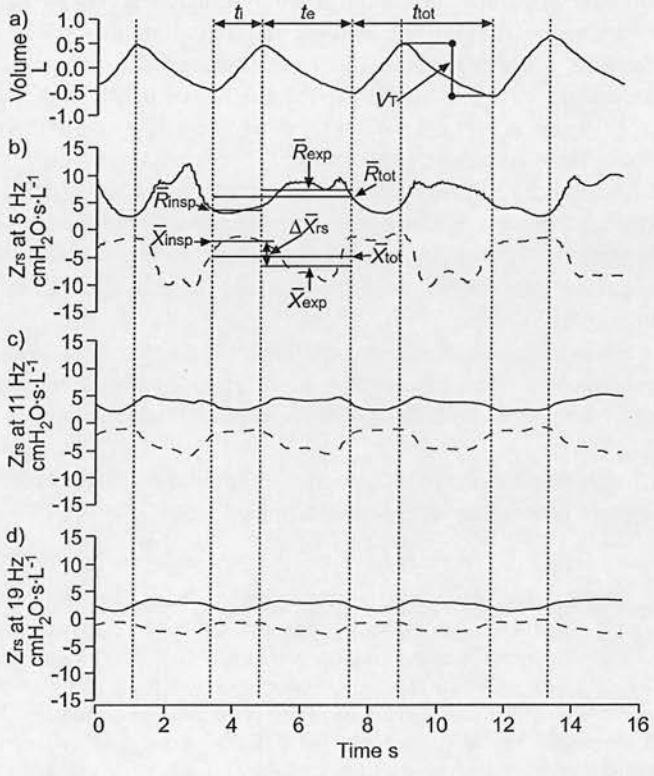

FIGURE 1. Examples of a representative experimental tracing of volume and within-breath multifrequency impedance from a chronic obstructive pulmonary disease patient with the definition of the indices considered in our study. a) Volume measured by integration of flow at the mouth. b)–d) Within-breath respiratory impedance (Z_{rs}) at 5 Hz (b), 11 Hz (c) and 19 Hz (d). Each impedance is expressed as respiratory system resistance (R_{rs}, ———) and reactance (X_{rs}, -------). The presence of large within-breath variation of X_{rs} with more negative values showed during expiration is a clear sign of the presence of expiratory flow limitation. t_i: inspiratory time; t_e: expiratory time; t_{tot}: total cycle duration; V_T: tidal volume; $\bar{R}_{exp}$: mean expiratory resistance; $\bar{R}_{tot}$: mean whole-breath resistance; $\bar{R}_{insp}$: mean inspiratory resistance; $\bar{X}_{insp}$: mean inspiratory reactance; $\Delta\bar{X}_{rs}$: difference between $\bar{X}_{insp}$ and $\bar{X}_{esp}$. $\bar{X}_{tot}$: mean whole breath reactance; $\bar{X}_{exp}$: mean expiratory reactance.

PRN signals, and to keep the total energy of the PRN signal low, the relative amplitude of the 5 Hz component of the PRN has been slightly increased.

The experimental set-up for forced oscillation technique (FOT) measurement was similar to that described previously [13]. The pressure signal generated by a loudspeaker was transferred from the box to the subject's mouthpiece through a connecting tube (22 cm long, 19 mm internal diameter). A low-resistance, highly inert tube (1.5 m long, 22 mm internal diameter) in parallel with the loudspeaker allowed the subjects to breathe room air without significant loss of forcing pressure. A bias flow of ~15 $L \cdot min^{-1}$ reduced the equipment dead space to the volume of the pneumotachograph and the mouthpiece [22]. The frequency response of the whole measuring system was assessed up to 30 Hz, as described previously [2], and was flat.

Experimental protocol

Patients attended on one occasion, when all measurements were made in the same order. Plethysmographic lung volume measurements were followed by recording oscillatory mechanics at 5 Hz and breathing pattern with the patients seated, wearing a nose-clip and with an operator firmly supporting the cheeks to reduce upper airways shunt [23]. The patients breathed spontaneously through the FOT system for 1 min, then performed an IC manoeuvre and resumed spontaneous breathing.

After 10-min rest with the patient disconnected from the measuring circuit, the FOT measurements were repeated by following the same sequence of manoeuvres, but with the multifrequency PRN signal applied.

Next, patients received 5 mg of nebulised salbutamol from an oxygen-driven Acorn® nebuliser (MedicAid, Pagham, UK) and after 45 min of spirometry, plethysmography and the two FOT measurements were repeated as described previously.

Data analysis

Within-breath respiratory system input impedance (Z_{rs}) was determined by using a least squares algorithm taking advantage of the *a priori* knowledge of the frequency spectrum components of the forcing signals [24, 25].

From the complete FOT recording and impedance tracing, we selected ~10 breaths starting from 45 s after the first IC, to avoid possible alterations of the breathing pattern after the manoeuvre. Breaths in which Z_{rs} tracings showed spikes or oscillations due to swallowing or glottis closure were discarded. For each breath, the values of several breathing pattern parameters and Z_{rs} indices were computed and averaged for all the breaths in each subject and condition. Within-breath respiratory system resistance (R_{rs}) was characterised by the mean values it assumed during inspiration, expiration and during the whole breath ($\overline{R}_{insp}$, $\overline{R}_{exp}$ and $\overline{R}_{tot}$, respectively). As the frequency dependence of R_{rs} is related to the heterogeneity of airway obstruction [22, 26], we also computed the difference between R_{rs} measured at our lowest and highest frequency (5 and 19 Hz, $\overline{R}_5$–$\overline{R}_{19}$).

Respiratory system reactance (X_{rs}) was characterised by its average value during a breath and its within-breath fluctuations were quantified by computing its average value during inspiration ($\overline{X}_{insp}$) and expiration ($\overline{X}_{exp}$). Their difference ($\Delta\overline{X}_{rs}=\overline{X}_{insp}-\overline{X}_{exp}$) was used to detect EFL. A breath was considered flow-limited if $\Delta\overline{X}_{rs}$ was greater than a threshold of 2.8 $cmH_2O \cdot s \cdot L^{-1}$, a value that in our previous studies [2, 13, 14], enabled identification of flow-limited breaths with very high sensitivity and specificity. A subject was classified as flow-limited if the majority of his selected breaths were flow-limited.

Data are expressed as mean±SD, unless otherwise stated. All data comparisons were made relative to that individual's baseline value, although we did conduct an exploratory analysis of the spirometry data based on the reversibility criteria recommended by the American Thoracic Society (ATS)/ERS to identify bronchodilator responsiveness (FEV_1 change >12% from the baseline and >200 mL) [27]. Significant differences in the physical characteristics, spirometric data, and R_{rs} and X_{rs} indices values of the different groups were evaluated using paired or unpaired t-tests, as appropriate. To allow for the multiple comparisons to be made between groups, only $p<0.01$ was considered to be statistically significant. Our primary outcome was the change in IC after administration of the bronchodilator. We calculated that a study with 15 patients would have an 80% chance of showing a difference of 200 mL at the 5% significance level between the groups. As we anticipated identifying flow-limited and nonflow-limited patients, we aimed to recruit 40 individuals to increase our ability to detect differences between the subgroups.

RESULTS

The baseline characteristics of the 42 COPD patients recruited in this study are reported in table 1. All patients performed the measurements correctly, with no reports of discomfort. From these patients, a total of 788 breaths were selected and analysed (408 before and 380 after bronchodilator). In figure 1, an experimental tracing of volume and multifrequency impedance data are shown for a representative flow-limited patient. The presence of flow limitation is clearly shown by the large decrease of X_{rs} during expiration compared with inspiration. Figure 1 also shows that the presence of EFL affects within-breath variations of Z_{rs} at all frequencies but, as predicted by the model simulation [13], the intra-breath X_{rs} swings decrease in amplitude with increasing frequencies.

The 5 Hz component of the multifrequency forcing gave similar results to those of the single 5 Hz frequency and, therefore, in the rest of this study only data recorded during multifrequency forcing are reported. A full account of the comparison of the single and multifrequency testing is presented in the online supplementary material.

Group mean data post-bronchodilator without accounting for tidal expiratory flow limitation

The lung function, breathing pattern and impedance indices for the whole patient group, measured after the bronchodilator are presented in tables 1 and 2. Bronchodilation (BD) produced statistically significant improvements in all the measured plethysmographic variables except for FEV_1/FVC and TLC (table 1). There was a significant increase in V'_E and a fall in mean inspiratory and expiratory flow (table 2).

TABLE 1 Patient characteristics and lung function before and after bronchodilation (BD)

	Pre-BD	Post-BD	p-value
Age yrs	63.7±8.4		
Sex M/F	21/23		
Weight kg	68.3±21.6		
Height cm	163.9±9.0		
FEV1			
L	1.12±0.39	1.31±0.46	<0.001
% pred	42.28±13.82	49.08±15.87	<0.001
FEV1/FVC	46.81±10.75	46.23±11.59	0.510
FVC			
L	2.42±0.68	2.86±0.76	<0.001
% pred	68.69±14.26	80.99±15.14	<0.001
SVC			
L	2.60±0.70	2.95±0.83	<0.001
% pred	73.01±12.64	82.78±16.33	<0.001
IC			
L	1.85±0.52	2.09±0.62	<0.001
% pred	72.95±17.94	81.51±18.92	<0.001
RV			
L	4.82±1.31	4.50±1.15	<0.001
% pred	235.00±59.04	219.99±50.84	<0.001
TGV			
L	5.62±1.48	5.35±1.37	<0.001
% pred	184.49±36.19	175.60±34.23	<0.001
TLC			
L	7.50±1.72	7.44±1.65	0.228
% pred	131.74±20.03	130.86±17.73	0.175

Data are presented as mean± SD, unless otherwise indicated. M/F: male/female; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; SVC: slow vital capacity; IC: inspiratory capacity; RV: residual volume; TGV: thoracic gas volume; TLC: total lung capacity.

In total, 18 patients met the ATS/ERS criteria for reversibility of airway obstruction. There were no differences between responder and nonresponder groups in their baseline plethysmographic or oscillatory variables. The changes in plethysmographic variables post-bronchodilator were similar for the two spirometrically defined groups, while the oscillometric indices differed between the responders and nonresponders. Specifically $\bar{R}_{tot}$ and $\bar{R}_{insp}$ at 5 Hz and mean difference in resistances at 5 and 19 Hz ($\bar{R}_5$–$\bar{R}_{19}$) fell significantly more (p=0.002, p=0.001 and p=0.002, respectively), while no differences were seen in X_{rs} between the groups. The discriminative power tested by the receiver operated characteristic curves was greater when $\bar{R}_{insp}$ was used compared with $\bar{R}_{tot}$ (80.1% and 73.5%, respectively) [28]. More details on lung volumes, breathing pattern and Z_{rs} data for responders and nonresponders groups are shown in table E4 in the online supplementary material.

In general, changes in X_{rs} indices were statistically significant at all forcing frequencies, while the fall in R_{rs} only occurred consistently when measured during inspiration. As a result $\bar{R}_{tot}$ only decreased significantly relative to baseline at 5 Hz while $\bar{R}_{exp}$ did not change significantly at any frequency.

TABLE 2 Breathing pattern and within-breath input impedance measured at 5 Hz data for patients before and after bronchodilation (BD)

	Pre-BD	Post-BD	p-value
$\dot{V}'_E$ L·min^{-1}	11.036±3.465	12.053±3.731	<0.001
V_T L	0.656±0.240	0.711±0.244	0.014
f_R breaths·min^{-1}	18.1±5.6	18.1±5.4	0.936
t_i s	1.375±0.473	1.373±0.540	0.975
t_{tot} s	3.747±1.525	3.743±1.633	0.968
t_i/t_{tot}	0.376±0.057	0.375±0.055	0.723
V_T/t_i L·s^{-1}	0.500±0.169	0.545±0.167	<0.001
V_T/t_E L·s^{-1}	0.299±0.095	0.327±0.108	0.001
$\bar{R}_{insp}$	5.1±1.6	4.2±1.5	<0.001
$\bar{R}_{exp}$	6.2±2.5	5.8±2.7	0.036
$\bar{R}_{tot}$	5.8±2.1	5.2±2.2	0.001
$\bar{X}_{insp}$	-2.3±1.2	-1.8±1.1	<0.001
$\bar{X}_{exp}$	-5.3±4.3	-3.8±3.3	0.001
$\bar{X}_{tot}$	-4.3±3.3	-3.1±2.5	0.001
$\Delta\bar{X}_{rs}$	2.9±3.4	2.0±2.5	0.004
$\bar{R}_5$–$\bar{R}_{19}$	1.8±1.0	1.2±0.9	<0.001

Data are presented as mean±SD, unless otherwise indicated. Impedance data (R and X) are expressed as cmH_2O·s·L^{-1}. $\dot{V}'_E$: minute ventilation; V_T: tidal volume; f_R: respiratory frequency; t_i: inspiratory time; t_{tot}: total cycle duration; t_i/t_{tot}: inspiratory duty cycle; V_T/t_i: mean respiratory flow rate; V_T/t_E: mean expiratory flow rate; $\bar{R}_{insp}$: mean inspiration resistance; $\bar{R}_{exp}$: mean expiration resistance; $\bar{R}_{tot}$: mean whole breath resistance; $\bar{X}_{insp}$: mean reactance during inspiration; $\bar{X}_{exp}$; mean reactance during expiration: $\bar{X}_{tot}$: mean total reactance ; $\Delta\bar{X}_{rs}$: mean difference in reactance; $\bar{R}_5$–$\bar{R}_{19}$: mean difference in resistances at 5 and 19 Hz.

Considering all the patients, $\bar{R}_{insp}$ at 5 Hz was statistically greater than at 19 Hz both before and after BD. However, it was possible to identify a subgroup of seven patients in which this difference was statistically different before BD (p=0.008), but not after (p=0.204) BD. These patients were, on average, less obstructed (FEV1 was 56.6±16.02 % predicted (% pred) pre- and 66.9±18.6 % pred post-BD) than the others, enforcing the concept that $\bar{R}_5$–$\bar{R}_{19}$ can be used as a sensitive index of heterogeneity in airway obstruction. Indeed, $\bar{R}_5$–$\bar{R}_{19}$ showed a statistically significant decrease, suggesting that the pattern of airway obstruction was on average more homogeneous after BD (table 2, fig. 2).

Effects of expiratory flow limitation on pre- and post-bronchodilator lung function and impedance measurements

Of the 42 patients, 20 were flow-limited at rest pre-bronchodilator and EFL was present in the majority of breaths studied both before and after BD (fig. 3).

At baseline, FEV1 was clearly lower and RV higher in the flow-limited patients, but the differences in other plethysmographic variables did not reach our adjusted significance level.

Of the oscillometric measurements $\bar{R}_{insp}$, $\bar{R}_5$–$\bar{R}_{19}$ and all the reactance indices were greater in the flow-limited patients,

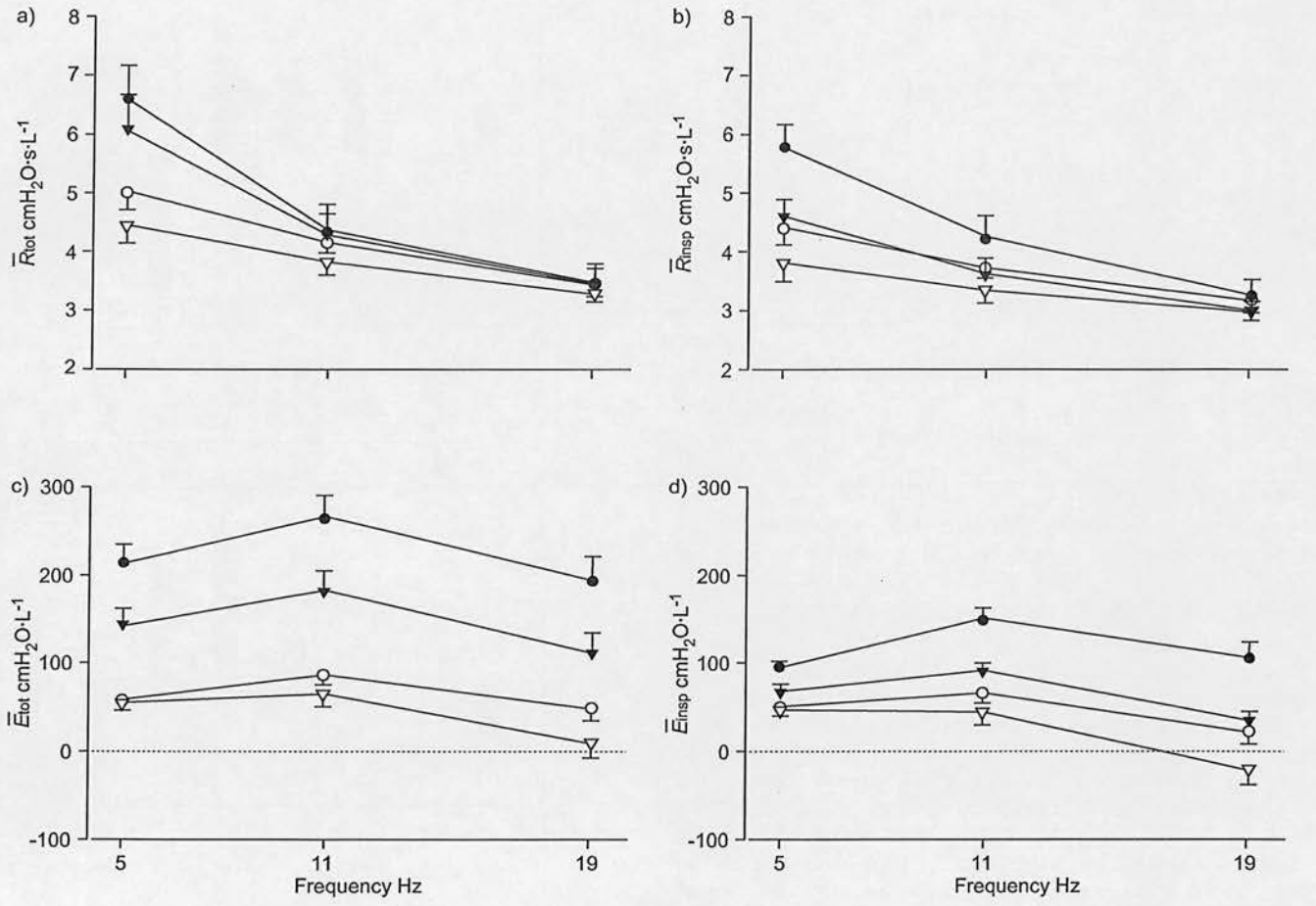

FIGURE 2. Multifrequency impedance spectra for a) mean whole breath resistance ($\bar{R}_{tot}$), b) mean inspiration resistance ($\bar{R}_{insp}$), c) mean whole breath respiratory elastance at 5 Hz ($\bar{E}_{tot}$) and d) mean inspiratory elastance at 5 Hz ($\bar{E}_{insp}$) in flow-limited (closed symbols) and nonflow-limited (open symbols) patients at baseline before (circles) and after (triangles) bronchodilation.

with nonsignificant differences being seen in the other resistance measurements.

Post-bronchodilator, both groups improved in all spirometric and lung volume variables except for FEV1/FVC and TLC (table 3, fig. 4a). There were significant decreases in $\bar{R}_{insp}$ and $\bar{R}_{tot}$ in patients with EFL, but not in those without EFL where the pre-bronchodilator values for these variables were significantly lower (table 3, fig. 4b). X_{rs} was significantly less negative after BD at all frequencies in flow-limited patients, while in nonflow-limited subjects, the change in X_{rs} was significant only at high frequencies.

The effect of flow limitation on indices of lung homogeneity pre- and post-BD

To further investigate the effect of the bronchodilator without the confounding effect of expiratory flow limitation, we considered both $\bar{R}_{tot}$ and $\bar{R}_{insp}$, and dynamic elastance (*i.e.* X_{rs} multiplied by $-2\pi f$, where f is the forcing frequency) over the forcing frequencies used in this study (fig. 2). Unlike patients without flow limitation, EFL patients showed a clear pattern of frequency dependence that became more evident when the expiratory phase was excluded. After the bronchodilator, R_{rs} decreased at all frequencies in nonflow-limited patients, and the changes were similar whether $\bar{R}_{tot}$ or $\bar{R}_{insp}$ data were selected. By contrast, the change in R_{rs} was much more evident (and statistically significant) in EFL patients when $\bar{R}_{insp}$ was used (fig. 2).

Effects of a bronchodilator on the presence of expiratory flow limitation

Of the 20 flow-limited patients at baseline, eight patients became nonflow-limited after BD, while no patient initially without EFL developed it. The patients where flow limitation was abolished had nonsignificantly different $\Delta\bar{X}_{rs}$ values at baseline and changes in the $\Delta\bar{X}_{rs}$ after salbutamol compared with those patients where flow-limitation persisted. There was no relationship between inspiratory capacity and $\Delta\bar{X}_{rs}$ changes overall in the flow-limited patients (r=0.107).

DISCUSSION

The development of expiratory flow limitation during tidal breathing identifies a group of COPD patients whose ability to increase their V_T to maintain gas exchange is significantly

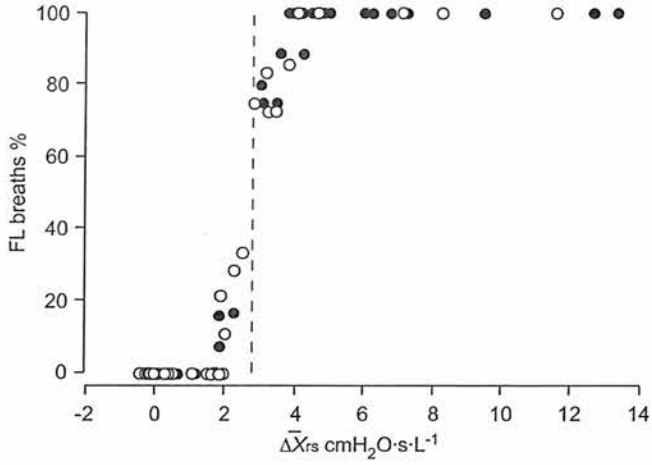

FIGURE 3. Relationship between the average value of mean difference in respiratory system reactance ($\Delta\bar{X}$rs) and the percentage of individually classified flow-limited (FL) breath for each patient before (●) and after (○) bronchodilation.

limited [29]. Inhaling a bronchodilator drug can potentially have multiple effects in COPD, which may be influenced by the presence of tidal EFL. These include a reduction in airways' resistance, an abolition of EFL at that operating lung volume or a shift in the distribution of choke points within the lung, all of which can lead to a fall in end-expiratory lung volume that in turn may lead to the persistence of EFL at rest. We used the forced oscillation method to identify the presence of expiratory flow limitation on a breath-by-breath basis, to measure respiratory system mechanics during tidal breathing and to quantify the heterogeneity of lung obstruction in COPD. To do this we used a within-breath multifrequency method that allowed us to assess the heterogeneity of the obstruction [26, 30], and produced comparable data to that measured using the single frequency approach. Our data in a more homogeneous patient group suggest that the response to bronchodilators is more complex than initially proposed [10].

The effect of the high dose β-agonist on resting lung mechanics and breathing pattern we observed in the group as a whole was similar to that reported in other studies of hyperinflated COPD patients [5, 9, 31], with significant increases in FEV1 and inspiratory capacity and falls in RV and TGV. $\dot{V}'$E increased, as did mean inspiratory and expiratory flow rates, compatible with the decrease in total and inspiratory resistance. Bronchodilator reversibility defined spirometrically is common in COPD [32]. Although nearly half of our patients met the current criteria for a response [27], there was no difference in the magnitude of the IC change in spirometric responders and nonresponders, which helps to explain why these tests are only poorly predictive of the patient's subsequent clinical course [6, 7, 33]. However, oscillatory mechanics changed differently in responders and nonresponders, with the Rrs values tracking the changes in FEV1, unlike the reactance values, which followed the inspiratory capacity data. A similar discrepancy between resistance and reactance measurements pattern has been reported during recovery from COPD exacerbations [34, 35], where changes in breathlessness follow those in inspiratory capacity.

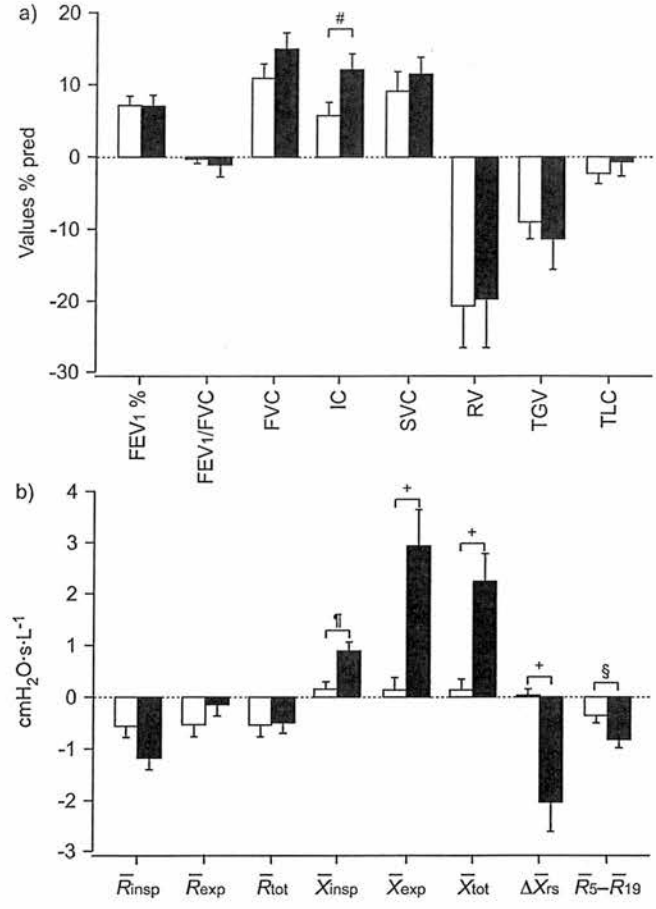

FIGURE 4. Changes of a) spirometric, plethysmographic, and b) impedance data at 5 Hz induced by bronchodilator in flow-limited (□) and nonflow-limited (■) patients at baseline. % pred: % predicted; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; IC: inspiratory capacity; SVC: slow vital capacity; RV: residual volume; TGV: thoracic gas volume; TLC: total lung capacity; $\bar{R}$insp: mean inspiration resistance; $\bar{R}$exp: mean expiration resistance; $\bar{R}$tot: mean whole breath resistance; $\bar{X}$insp: mean reactance during inspiration; $\bar{X}$exp; mean reactance during expiration: $\bar{X}$tot: mean total reactance ; $\Delta\bar{X}$rs: mean difference in reactance; $\bar{R}$5–$\bar{R}$19: mean difference in resistances at 5 and 19 Hz. #: p=0.04; ¶: p=0.05; +: p=0.001; §: p=0.031.

Resting expiratory flow limitation was present in just over half the patients. All the breaths studied were consistently classified, except for eight cases where the degree of EFL varied from breath to breath and the classification was based on a majority decision. As expected, flow-limited patients had worse spirometry and a higher RV with a general tendency for higher lung volumes, although these differences were less consistent between groups. Despite this, the response to bronchodilators was almost identical with similar changes in flow and volume indices irrespective of the presence of flow limitation. This does not preclude a different behaviour during exercise in the patients who were flow-limited at rest, but the improvement in exercise performance post-bronchodilator has been consistently related to changes in resting inspiratory capacity, without reference to whether these occurred in flow-limited patients [33, 36].

TABLE 3 Lung function, breathing pattern and impedance data at 5 Hz for patients who were nonflow-limited (non-FL) at baseline and patients who were FL

	Non-FL at baseline		p-value	FL at baseline		p-value	Non-FL *versus* FL p-value#
	Pre-BD	Post-BD		Pre-BD	Post-BD		
FEV_1							
L	1.27±0.43	1.47±0.53	**<0.001**	0.95±0.27	1.14±0.30	**<0.001**	0.007
% pred	47.89±14.55	54.72±17.34	**<0.001**	36.10±10.07	43.15±11.89	**<0.001**	0.004
FEV_1/FVC %	50.27±10.59	50.36±11.52	0.504	43.00±9.81	41.90±10.24	0.380	**0.027**
FVC							
L	2.54±0.70	2.91±0.77	**<0.001**	2.28±0.65	2.80±0.77	**<0.001**	0.213
% pred	73.22±14.64	83.26±13.86	**<0.001**	63.70±12.32	78.60±16.38	**<0.001**	**0.029**
SVC							
L	2.61±0.72	2.90±0.83	**<0.001**	2.59±0.70	2.99±0.84	**<0.001**	0.943
% pred	74.47±13.56	82.77±16.16	**<0.001**	71.40±11.68	82.80±16.94	**<0.001**	0.439
IC							
L	1.85±0.53	2.01±0.66	**<0.001**	1.86±0.53	2.18±0.59	**<0.001**	0.969
% pred	75.72±18.47	81.04±19.28	**<0.001**	69.90±17.28	82.00±19.02	**<0.001**	0.299
RV							
L	4.29±1.21	4.02±0.98	**<0.001**	5.40±1.18	5.04±1.10	0.020	**0.004**
% pred	216.81±57.88	203.69±46.28	**<0.001**	255.00±54.92	238.11±50.72	0.015	**0.035**
TGV							
L	5.16±1.33	4.93±1.24	**<0.001**	6.14±1.49	5.84±1.39	0.019	**0.030**
% pred	172.53±33.05	164.73±31.44	**<0.001**	197.65±35.64	188.28±33.75	0.019	**0.023**
TLC							
L	7.02±1.66	6.97±1.61	0.261	7.99±1.67	7.97±1.57	0.747	0.070
% pred	125.46±19.76	124.48±17.33	0.184	138.65±18.38	137.94±15.73	0.703	**0.031**
Z_{rs} 5 Hz							
$\bar{R}_{insp}$	4.4±1.2	3.8±1.5	0.014	5.8±1.8	4.6±1.3	**<0.001**	**0.005**
$\bar{R}_{exp}$	5.4±1.5	4.9±1.6	0.032	7.0±3.0	6.9±3.3	0.511	0.038
$\bar{R}_{tot}$	5.0±1.4	4.5±1.5	0.024	6.6±2.5	6.1±2.6	0.020	0.013
$\bar{X}_{insp}$	-1.7±0.9	-1.5±1.1	0.318	-3.1±1.0	-2.2±1.1	**<0.001**	**<0.001**
$\bar{X}_{exp}$	-2.1±1.4	-2.0±1.7	0.601	-8.8±3.5	-5.8±3.4	**<0.001**	**<0.001**
$\bar{X}_{tot}$	-1.9±1.2	-1.8±1.5	0.527	-6.8±2.9	-4.6±2.6	**<0.001**	**<0.001**
$\Delta\bar{X}_{rs}$	0.4±0.7	0.4±0.8	0.860	5.7±3.0	3.7±2.7	**0.002**	**<0.001**
$\bar{R}_5$–$\bar{R}_{19}$	1.2±0.7	0.8±0.9	0.019	2.5±0.7	1.6±0.6	**<0.001**	**<0.001**

Data are presented as mean±SD, unless otherwise stated. Impedance data (R and X) are expressed as $cmH_2O \cdot s \cdot L^{-1}$. BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; SVC: slow vital capacity; IC: inspiratory capacity; RV: residual volume; TGV: thoracic gas volume; TLC: total lung capacity; Z_{rs}: within-breath respiratory system input impedance; $\bar{R}_{insp}$: mean inspiration resistance; $\bar{R}_{exp}$: mean expiration resistance; $\bar{R}_{tot}$: mean whole breath resistance; $\bar{X}_{insp}$: mean reactance during inspiration; $\bar{X}_{exp}$; mean reactance during expiration: $\bar{X}_{tot}$: mean total reactance ; $\Delta\bar{X}_{rs}$: mean difference in reactance; $\bar{R}_5$–$\bar{R}_{19}$: mean difference in resistances at 5 and 19 Hz. #: the p-values are reported for the paired comparison pre- and post-BD in each group and for the unpaired comparison between non-FL and FL at baseline. All values in bold are statistically significant.

The changes in oscillatory mechanics noted above were largely driven by changes in flow-limited patients, presumably because the fall in lung volume in the nonflow-limited patients compensated for any improvement in resting resistance or reactance. The fall in group mean R_{rs} in the flow-limited subjects was due mainly to a reduction in $\bar{R}_{insp}$ of the respiratory system.

Multifrequency testing generated large amounts of data, which have been retained for completeness along with the breathing pattern data as online supplementary material. In general, these showed qualitatively similar changes in response to the bronchodilator to the data measured at 5 Hz. We characterised the heterogeneity of the lung with an index of the frequency dependence of resistance, $\bar{R}_5$–$\bar{R}_{19}$. It is possible to identify at least four different sources of heterogeneity: serial distribution of airway geometry [37], heterogeneous parallel airway constriction pattern [38], airway wall shunting [30], and heterogeneity of alveolar tissue in heterogeneous parenchymal diseases, such as emphysema [39]. Serial distribution of airway geometry affects impedance data mainly for frequencies >100 Hz, providing only negligible contribution at the forcing frequencies used in this study [40]. Tissue heterogeneity should not be affected by the administration of BD. As the frequency dependence of R_{rs} changed statistically significantly after bronchodilator application in most of the patients, with

some of them showing no frequency dependence at all after BD, the tissue heterogeneity should not be the dominant mechanism affecting $\overline{R}5$–$\overline{R}19$. Parallel airway constriction and airway wall shunting are not easy to differentiate, and it is likely that they are all together contributing to the definition of $\overline{R}5$–$\overline{R}19$.

Between-frequency comparisons showed that nonflow-limited patients had a relatively homogeneous distribution of resistance, and their response to the bronchodilator was similar whether $\overline{R}_{tot}$ or $\overline{R}_{insp}$ was plotted. By contrast, flow-limited patients showed a much greater frequency dependence at baseline, suggesting a highly heterogeneous pattern of obstruction. This pattern was apparently little affected by the bronchodilator when total R_{rs} was considered. However, a clear fall in frequency dependence of R_{rs} was evident when inspiratory data, unaffected by the artefacts due to EFL, were used. This suggests that BD has a great effect in homogenising time constants throughout the airway tree in flow-limited patients, as also supported by the changes in dynamic elastance with frequency, which are also in agreement with the model prediction of LUTCHEN *et al.* [26].

In some patients, bronchodilators abolished expiratory flow limitation in all or in the majority of breaths. This has been seen in other reports [31], although the potential for breath-to-breath variation in the presence of flow limitation complicates the interpretation of data when only a few breaths are sampled, as with the negative expiratory pressure method for identifying EFL. This subset of patients did not differ either in their baseline physiological characteristics before testing or in their degree of within-breath reactance change either before or after treatment.

Our data have some limitations. All studies were conducted at rest and seated, and changes in lung mechanics may not translate to data during exercise, although as already noted there is a good relationship between resting operating lung volumes and exercise performance. Oscillatory signals can be influenced by the shunt compliance provided by the upper airway in COPD. However, each subject is their own control in our data before and after the bronchodilator. Changes related to technical factors, such as the presence of expiratory flow limitation, provide a plausible explanation for the limited bronchodilator response previously reported in COPD using total Z_{rs} data and attributed to upper airway factors [15]. Our data have been reported using the multifrequency pseudo-random noise signal, which might have yielded different results to previous single frequency oscillation studies. However, as indicated in the online supplementary material, any differences seen with the systems are likely to relate to physiological differences between breath variation in the degree of flow limitation rather than systematic methodological error. This issue is considered in more detail in the online supplementary material.

In summary, expiratory flow limitation during tidal breathing has an important influence on the changes in resting lung mechanics after bronchodilator drugs in COPD, but it does not predict the magnitude of the subsequent improvement in operating lung volume, at least not at rest. Noninvasive measurements of tidal lung mechanics using the forced oscillation method are an attractive alternative to more usual effort dependent tests of pulmonary function and others have shown that such tests are a sensitive way of detecting bronchodilator effects in these patients [41]. However, the change in the total Z_{rs} after a bronchodilator may underestimate the true effects of therapy if expiratory impedance data are not excluded from the analysis in flow-limited patients. Despite these limitations, forced-oscillation data add considerable insight into the way treatment works in COPD and, as a noninvasive, effort-independent methodology, is well suited for monitoring patients in clinical settings where reliable clinical measurement has until now been difficult.

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Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease

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Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. J.G. Hay, P. Stone, J. Carter, S. Church, A. Eyre-Brook, M.G. Pearson, A.A. Woodcock, P.M.A. Calverley.

ABSTRACT: Partial bronchodilator reversibility can be demonstrated in many patients with stable chronic obstructive pulmonary disease (COPD), but its relevance to exercise capacity and symptoms is uncertain. Previous data suggest that anticholinergic bronchodilators do not improve exercise tolerance in such patients.

We studied 32 patients with stable COPD, mean age 65 yrs, in a double-blind, placebo-controlled, cross-over trial of the inhaled anticholinergic drug, oxitropium bromide. From the within and between day placebo spirometry, we derived the spontaneous variation in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) of this population (FEV_1 140 ml; FVC 390 ml) and considered responses beyond this to be significant.

Oxitropium bromide increased baseline FEV_1 from 0.70 (0.28) *l* (mean (SD)) to 0.88 (0.36) *l*. The 6 min walking distance increased by 7% compared with placebo, whilst resting breathlessness scores fell from 2.0 to 1.23 at rest and 4.09 to 3.28 at the end of exercise after the active drug.

Improvements in walking distances and symptoms were unrelated to changes in either FEV_1 or FVC, indicating that routine reversibility testing is not a good predictor of symptomatic benefit in these patients.

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Many patients with stable chronic obstructive pulmonary disease (COPD) show some reversibility of their airflow limitation on testing with beta-adrenergic or anticholinergic drugs [1–3], and some of these respond to corticosteroids [4–6]. Whilst the benefits of treatment associated with large changes in pulmonary function are clear in asthmatic patients [7], the smaller changes seen with partial reversibility in COPD are harder to evaluate. In particular, we do not know whether the improvements in breathlessness or exercise tolerance are confined to patients whose bronchodilator response exceeds the normal between measurement variability.

Inhaled anticholinergic bronchodilators appear to be more effective in older patients with less labile airflow limitation [2, 8, 9] but, unlike salbutamol, they did not improve corridor walking distance in a previous study [10]. We have investigated this unexpected finding in a double-blind, placebo-controlled, cross-over study of the effects of the anticholinergic drug, oxitropium bromide, on corridor walking distance and symptoms. In addition, we have established the spontaneous variability of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) in these patients, and using the data have examined the relationship between short-term bronchodilator response and changes in both exercise performance and dyspnoea, using different reversibility criteria.

Methods

We studied 32 patients in two centres. Chronic obstructive pulmonary disease was defined as a history of continuous breathlessness for more than 12 months together with an FEV_1 of ≤1.2 *l*. Patients with known cardiac or other respiratory disorders were excluded, as were those with exacerbations in the last two months and those taking oral corticosteroids. All subjects had been shown to have a >15% improvement in FEV_1 after inhaled salbutamol at sometime in the preceding six months and no change was made in their normal drug therapy during the study. No patient was receiving oral prednisolone. The mean age (SD) of the group was 65 (8) yrs, 17 were female, 7 were current smokers, 21 ex-smokers and 4 nonsmokers. Informed consent was obtained in all cases and the study protocol was approved by the District Ethics Committees of both hospitals.

Each patient attended on four occasions, at the same time of day, and at least 6 h after any inhaled bronchodilator treatment, (oral bronchodilators were discontinued seven days before entry to the study). All spirometric measurements were made with the dry spirometer (Vitalograph UK Ltd) recording the best FEV_1 and best FVC of three acceptable traces. Breathlessness was assessed by asking the patients "how breathless do you feel?" and recording the response on a modified Borg category scale [11]. Six minute walks (6MD) were performed as described by BUTLAND *et al.* [12] with a standardized encouragement during the walk. On the first two visits, spirometry was measured before and 15 min after salbutamol 200 μg or 45 min after ipratropium bromide 40 μg, both given by metered dose inhaler under supervision. Two practice 6 min walks were performed with 60 min rest between each walk. Breathlessness was assessed before and immediately after each walk (end-exercise). On visits 3 and 4, baseline spirometry was recorded and patients performed a walking test, as previously. Then, patients received either oxitropium bromide 200 μg or placebo from a metered dose inhaler in a randomized, double-blind fashion and, after 45 min, spirometry and the 6 min walk were repeated.

In assessing reversibility, we considered that significant change after a bronchodilator was likely when the spirometric variable (either FEV_1 or FVC) increased by 15% from its baseline value and this change exceeded the 95% confidence intervals for the variable in this population. Four patterns of response were possible - an isolated improvement in FEV_1 but not FVC, in FVC but not FEV_1, in both or in neither. We derived the spirometric confidence intervals for the population using the method described by TWEEDALE *et al.* [13]. Results are expressed as mean and standard deviation unless otherwise stated. Comparisons between treatments have been made using the paired Student's t-test as part of a general linear model analysis programme; p=0.02 being taken as the lower limit of significance [14]. The modified Borg scale linearizes the relationship between sensation and other physical variables within an individual [15]. Changes within individuals have been compared using both parametric and non-parametric tests (Wilcoxon signed rank) and no difference was seen between them. Statistical comparisons of Borg scale data between the subjects have been made using only non-parametric tests.

Results

There were no differences attributable to either the centre in which the study was conducted or to treatment order for any of the variables assessed. Mean walking distance increased significantly from 370 (82) to 401 (75) m between practice days 1 and 2 ($p<0.001$), but there was no further increase in baseline walking distance after day 2. Data describing the natural variability of these variables is presented for days 3 and 4 only, in order to exclude any practice effects.

Spontaneous measurement variation

The group mean baseline FEV_1 were very similar on days 3 and 4 (0.70 (0.28) *l* and 0.72 (0.28) *l*, respectively). Likewise, baseline FVC was stable at 1.74 (0.60) *l* and 1.72 (0.72) *l* on each day. Data describing the within and between day variability in spirometry, walking distance and breathlessness scoring were derived from measurements on the placebo day, before and after drug administration as appropriate. In this population a change of 140 ml in FEV_1 and 390 ml in FVC was required to exceed the within day 95% confidence intervals for these measurements. These values exceeded 15% of the baseline FEV_1 in these patients.

Likewise, baseline walking distance and resting breathlessness scores did not differ between the study days. The within day variation in walking distance was 53 m with a between day variability of 78 m. The non-parametric nature of the breathlessness scoring across the population makes a similar analysis for these variables inappropriate but there was no change in the group mean breathlessness score before and after placebo walks.

Bronchodilator effects

Group mean spirometry before and after salbutamol, ipratropium bromide and oxitropium bromide is reported in table 1, with the individual data interrelationships shown in figure 1. All three drugs produced a statistically significant bronchodilatation for the group as a whole but there was considerable variation in the size of these responses between subjects and across the different drugs. Oxitropium bromide increased group mean 6MD by 27 m, reduced breathlessness at rest scores from 2.02 to 1.23 and end-exercise scoring from 4.09 to 3.28 ($p<0.01$ in all cases compared with pre-drug values and placebo data (fig. 2)). However, the absolute increase in breathlessness scored during the walks before and after oxitropium bromide was not different.

In table 2 the characteristics of patients showing different patterns of bronchodilatation to oxitropium bromide are summarized. Approximately one third of the group showed no response spirometrically, one third responded with changes in both FEV_1 and FVC and one third with one or the other. Non-responders had a lower initial FEV_1, higher level of resting breathlessness and shorter baseline 6MD than complete responders. Statistically significant improvements in walking distance and reductions in breathlessness scores were seen in all three groups, with a similar absolute change in these variables occurring in the non-responder and complete responder subgroups. The absolute change in walking distance was not dependent on the size of the increase in FEV_1 but was inversely correlated with the change in resting breathlessness score, so that the greater the reduction in dyspnoea, the further the patient walked ($r=-0.44$, $p<0.01$).

Table 1. – Changes in group mean (SD) spirometric variables after placebo and the three inhaled bronchodilator drugs; each drug was administered on a different day

	FEV_1 *l*		FVC *l*	
	Before	After	Before	After
Placebo	0.72 (0.28)	0.73 (0.31)	1.74 (0.67)	1.69 (0.72)
Salbutamol	0.69 (0.27)	0.90 (0.34)*	1.62 (0.67)	2.10 (0.80)*
Ipratropium	0.71 (0.27)	0.88 (0.35)*	1.71 (0.69)	2.09 (0.86)*
Oxitropium	0.70 (0.28)	0.88 (0.36)*	1.72 (0.71)	2.13 (0.81)*

*: statistically significant difference at the $p<0.001$ level. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

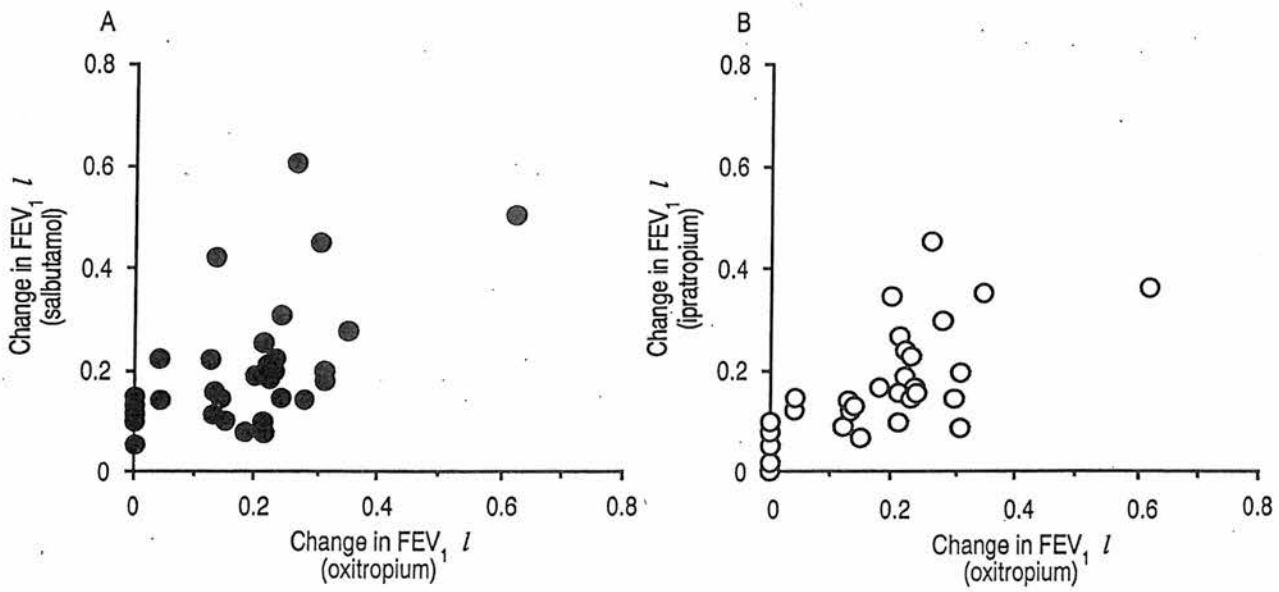

Fig. 1. – Individual data showing the interrelationship between the bronchodilator response to oxitropium with: A) 200 μg salbutamol; and B) 40 μg ipratropium bromide, and the variability of the response with three drugs.

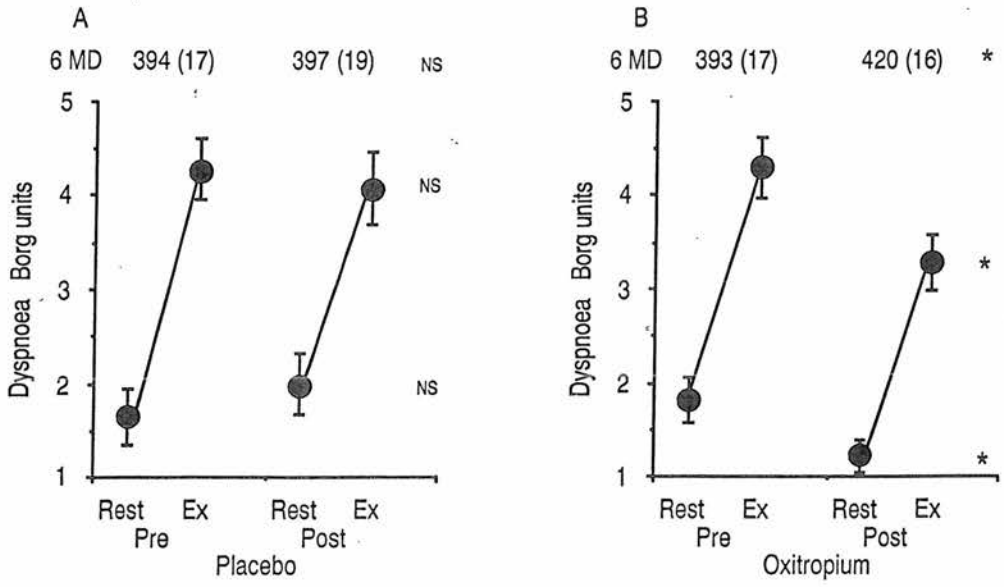

Fig. 2. – The effect of oxitropium bromide (B) on 6 min walking distance (6MD) and breathlessness scores compared with placebo (A). Data expressed as group mean (SEM). Error bars are included with breathlessness scores as a measure of variability and do not reflect the statistical treatment of the data. *: significantly different at the 1% level in the paired comparisons of walking distance, rest and exercise dyspnoea before and after drug. Ex: end-exercise.

Table 2. – Relationship of the bronchodilator response to walking distance and symptoms

Response Criterion	n	Baseline FEV_1 *l*	Baseline 6MD m	After bronchodilator ΔFEV_1 *l*	After bronchodilator ΔFVC *l*	After bronchodilator $\Delta 6MD$ m	Δ Dyspnoea Rest	Δ Dyspnoea End-exercise
FEV_1 + FVC	10	0.80 (0.33)	441 (101)	0.30 (0.12)	0.76 (0.36)	26 (37)	-0.6	-1.0
FEV_1 only	6	0.74 (0.29)	417 (52)	0.24 (0.02)	0.26 (0.15)	19 (16)	-0.6	-1.1
FVC only	3	0.57 (0.12)	348 (58)	0.14 (0.01)	0.44 (0.02)	15 (48)	-0.2	-0.7
Neither	13	0.60 (0.16)	358 (100)	0.06 (0.07)	0.19 (0.13)	33 (32)	-0.7	-1.1

Response criteria are defined by a change (Δ) in spirometry which exceeds the 95% confidence intervals for short-term variation in the measure. Responder groups are separated by the presence or absence of changes in FEV_1 and/or FVC. Data for the mean (SD) baseline FEV_1 (*l*) and 6 min walking distance (6MD, m) are given for each responder group, as are the mean changes in these variables and breathlessness scores after oxitropium bromide. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

Discussion

Several studies have demonstrated that patients with stable COPD can show significant improvements in spirometry after inhaled β_2-agonists [16] or anticholinergic drugs [17]. Control of bronchomotor tone in such patients appears to be cholinergically mediated [18], is subject to day-to-day variation [3, 19] and may be important prognostically [20]. However, the absolute changes in spirometry are small, fall within the spontaneous variation of the measurement [13], and may not be relevant to symptoms or exercise performance. There is no general agreement about the best way to define clinically relevant spirometric changes in these patients and whether changes in FVC or peak expiratory flow are better predictors of improvement. Most investigators have selected criteria which give the best discrimination among the study population but this is not necessarily associated with symptomatic benefit [5, 6, 21]. We found that patients with stable COPD show small but significant improvements in breathlessness and corridor walking distance after inhaled oxitropium bromide but not placebo. These improvements were not confined to those classified as being reversible on spirometric criteria, but patients in whom both FEV_1 and FVC improved after bronchodilator had a higher baseline FEV_1 and a better initial walking distance.

Methodological problems limit the clinical application of the tests used in this study. Familiarization with the walking test is an important aspect of trial design [22] but unlike some other groups we found that after two pre-study visits there were no significant differences in the pre-drug walking distances. Quantification of respiratory sensations using visual analogue or category scaling is increasingly used in the assessment of treatment [23] and the modified Borg scale has the advantage of being linearly related to objective physiological measurements [14, 24]. In this study, breathlessness provided a complimentary endpoint and some individuals (n=11) walked for a similar distance but to a lower level of dyspnoea after active drug, whilst others (n=5) increased their 6MD and end-exercise level of breathlessness.

In defining a bronchodilator response, we were able to use our placebo data to establish the spontaneous variation of FEV_1 and FVC in our study population. We used an identical method to that described by TWEEDALE *et al.* [13] and obtained very similar results, suggesting a wider applicability for such values [5]. Adoption of different response criteria has a substantial effect on the numbers considered to be responsive [25] and we observed three subjects in whom FVC improved in isolation beyond our confidence limits.

Oxitropium bromide is an anticholinergic drug similar to ipratropium bromide and has its maximal bronchodilator effect between 30–90 min after inhalation [26]. A previous double-blind study of the effects of ipratropium bromide on exercise tolerance in 24 similar patients found no improvement in 12 min walking distance [10] but the present study is larger, involved more practice walks before the study days, used a different drug and quantified symptoms. Comparison with ipratropium bromide suggests that the dose of oxitropium bromide used would be higher on the dose response curve [26] and this may explain the somewhat greater increases in walking distance that we found. However, the impact of the active drug on symptoms was greater than that on walking distance with a reduction in both baseline and end-exercise levels of dyspnoea after oxitropium bromide. This emphasizes the importance of assessing symptoms as objectively as possible if important drug effects are to be detected. Although within the short-term reproducibility of this measure the change in 6MD was, nonetheless, statistically significant for the group. A small change in walking distance alone is of doubtful significance unless accompanied by parallel reductions in symptoms.

The rapid onset of action of inhaled adrenergic and anticholinergic bronchodilators has made short-term reversibility testing with spirometry practical in the clinic and the laboratory, but the interpretation of such tests is difficult because of spontaneous variation in baseline FEV_1 [3]. Although, all of the study patients had shown reversibility in FEV_1 prior to entry, only half would have been classified as having such reversibility when studied with our active drug. We did not find a relationship between baseline FEV_1 and 6MD, nor was the change in FEV_1 predictive of improvement in walking distance after oxitropium bromide. Reversibility status, however defined, had no effect on the

small but statistically significant increases in walking distance and reduction in breathlessness which occurred in these patients. This suggests that the FEV_1 response behaves as a continuous variable and that for these purposes the separation into "reversible" and "irreversible" patients is not helpful. These findings with anticholinergic blockade are similar to those reported in smaller studies, where patients were selected for lack of reversibility to β_2-agonists [27], and to a study which shows reduction in breathlessness at rest after bronchodilator in similar COPD patients [28]. Whether such changes would be present in patients who do not respond on repeated reversibility testing is not known.

Why these effects occur is unclear. The small degree of bronchodilatation produced by oxitropium bromide in the central airways [29–31] may be sufficient to permit better lung emptying during exercise. Alternatively, improvement may also affect small airway calibre, which might improve exercise tolerance, as has been suggested with other drugs, in similarly disabled patients [32]. Such an effect may influence the degree of hyperinflation at rest, reducing the inspiratory threshold load imposed by positive end-expiratory pressure (PEEPi), and hence diminish the perception of breathlessness. The mechanisms underlying this have recently been reviewed [33–35]. Anticholinergics might affect afferent information from intrapulmonary stretch receptors but the evidence for an important role for such a sensation in the perception of breathlessness in man, is presently lacking.

Whatever the mechanism, these data show that anticholinergic therapy can improve symptoms and exercise tolerance in COPD, even when the changes in spirometry fall within the expected variability of the measurement. Whilst tests of bronchodilator reversibility may help to categorize the patients and select a group more likely to be steroid responsive [5], failure to show a "reversible" response should not preclude a trial of symptomatic bronchodilator treatment.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Regional chest wall volumes during exercise in chronic obstructive pulmonary disease

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Background: Dynamic hyperinflation of the lungs impairs exercise performance in chronic obstructive pulmonary disease (COPD). However, it is unclear which patients are affected by dynamic hyperinflation and how the respiratory muscles respond to the change in lung volume.

Methods: Using optoelectronic plethysmography, total and regional chest wall volumes were measured non-invasively in 20 stable patients with COPD (mean (SD) forced expiratory volume in 1 second 43.6 (11.6)% predicted) and dynamic hyperinflation was tracked breath by breath to test if this was the mechanism of exercise limitation. Resting ventilation, breathing pattern, symptoms, rib cage and abdominal volumes were recorded at rest and during symptom limited cycle ergometry. Pleural, abdominal, and transdiaphragmatic pressures were measured in eight patients.

Results: End expiratory chest wall volume increased by a mean (SE) of 592 (80) ml in 12 patients (hyperinflators) but decreased by 462 (103) ml in eight (euvolumics). During exercise, tidal volume increased in euvolumic patients by reducing end expiratory abdominal volume while in hyperinflators tidal volume increased by increasing end inspiratory abdominal and rib cage volumes. The maximal abdominal pressure was 22.1 (9.0) cm H_2O in euvolumic patients and 7.6 (2.6) cm H_2O in hyperinflators. Euvolumic patients were as breathless as hyperinflators but exercised for less time and reached lower maximum workloads ($p<0.05$) despite having better spirometric parameters and a greater expiratory flow reserve.

Conclusions: Dynamic hyperinflation is not the only mechanism limiting exercise performance in patients with stable COPD. Accurate measurement of chest wall volume can identify the different patterns of respiratory muscle activation during exercise.

Exercise limitation is a major cause of disability in patients with chronic obstructive pulmonary disease (COPD) and is largely the result of disturbances in the mechanics of breathing. Tests of airflow limitation at rest such as forced expiratory volume in 1 second (FEV_1) are relatively poor predictors of exercise duration in these patients.[1 2] The most common explanation for this is that, unlike healthy subjects, end expiratory lung volume (EELV) increases during exercise in patients with COPD, decreasing the inspiratory capacity (IC).[2 3] This dynamic hyperinflation increases the ability of the respiratory system to generate expiratory flow but limits the maximum tidal volume and reduces the ability of inspiratory muscles to produce force by reducing their length, leading to the sensation of breathlessness.[4] At present few data are available on the time course of these changes, how the volume change is distributed between the compartments of the chest wall (rib cage and abdomen), and what happens in patients who do not show these changes in lung volume.

EELV is usually measured indirectly from IC, but this is influenced by the subject's ability to cooperate. It cannot follow breath-to-breath variation in lung volume. Integrator drift, which is multifactorial in origin, also poses a problem. This problem can be overcome by using optoelectronic plethysmography (OEP).[5 6] OEP is an accurate non-invasive method for measuring total chest wall volume (Vcw), ventilation, and respiratory kinematics.[7–10] It enables analysis of chest wall motion and accurately measures changes in the volume of the different respiratory compartments of the chest wall in different postures and conditions. Although OEP cannot measure the absolute lung volume unless the subdivisions of lung volume are also known, it can measure changes in volume such as during a tidal breath and can record breath by breath changes in EELV, as well as its distribution between the different chest wall compartments.[6]

A study was undertaken to measure operating chest wall volumes on a breath by breath basis in patients with clinically stable symptomatic COPD at rest and during exercise, and thus to assess how the chest wall changed as dynamic hyperinflation developed. We hypothesised that an increase in end expiratory Vcw would be the most important factor limiting exercise, but found a more complex situation than we anticipated.

METHODS

Subjects

Twenty men with stable COPD diagnosed by accepted criteria took part in the study.[11 12] All had been smokers and complained of exertional dyspnoea. None had clinical or physiological features of bronchial asthma or a history of exacerbation in the previous 6 weeks. There were no co-morbid conditions limiting exercise. Patients were studied before pulmonary rehabilitation and were unfamiliar with physiological exercise testing. Routine bronchodilator drugs were omitted for 4 hours (short acting) or 12 hours (long acting) before attendance. The

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; EELV, end expiratory lung volume; EEVcw, end expiratory chest wall volume; FEF, forced expiratory flow at a percentage of FVC; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; OEP, optoelectronic plethysmography; Pab, abdominal pressure; Pdi, transdiaphragmatic pressure; Pga, gastric pressure; Poes, oesophageal pressure; Ppl, pleural pressure; RV, residual volume; TLC, total lung capacity; Vab, abdominal volume; Vcw, total chest wall volume; Vrc, rib cage volume

protocol was approved by the district research ethics committee and informed consent was obtained.

Measurements

Subdivisions of lung volumes were measured by body plethysmography (Medgraphic Autolink 1085D, Medical Graphics, St Paul, MN, USA) using ATS standards.[13] Flow was measured at the mouth by a screen pneumotachograph and integrated to display the flow-volume loop from which FEV_1, FVC, and flow indices were derived.

Chest wall kinematics and compartmental volumes were non-invasively measured by OEP. The principle of this method is described in detail elsewhere.[5 6] Briefly, OEP measures the change in the complex shape of the chest wall during breathing by modelling the thoracoabdominal surface with a large number of points belonging to selected anatomical reference sites on the rib cage and abdomen. The three dimensional positions and displacements of each point are measured by a motion analyser (BTS, Milan, Italy) based on passive (reflective) markers (plastic hemispheres of 10 mm diameter covered by a thin film of retroreflective paper) placed on the skin using biadhesive hypoallergenic tape and special TV cameras operating up to 100 frames per second synchronised with coaxial infrared flashing LEDs. After computing and classifying the two dimensional coordinates of all markers surveyed by at least two TV cameras, the system determines the three dimensional coordinates of the different markers by stereo-photogrammetry. Once the three dimensional coordinates of the points belonging to the chest wall surface are acquired with reference to an arbitrary coordinate system, a closed surface is defined by connecting the points to form triangles (mesh of triangles) and the volume contained by the surface is computed using Gauss' theorem. This procedure allows the direct computation of the volume enclosed by the thoraco-abdominal surface approximated by a closed mesh of triangles. As in our previous studies, we used 89 markers placed over the chest wall surface and four TV cameras (two in front and two behind the subject at a distance of 3 m) to track their movement.

Eight patients were instrumented using standard balloon tipped catheters connected to pressure transducers (SCX05; Sensym, Milpitas, CA, USA) for recording oesophageal (Poes) and gastric (Pga) pressures which were used as indices of pleural (Ppl) and abdominal (Pab) pressures, respectively. Transdiaphragmatic pressure (Pdi) was computed as the difference between Pga and Poes. In these subjects we also continuously measured flow at the airway opening using a low dead space (70 ml) pneumotachograph (Medical Graphics).

Breath by breath oxygen consumption and carbon dioxide production were measured using a fuel cell and infrared carbon dioxide analyser, respectively, as part of a commercial exercise system (Medical Graphics).

Pressures and flow signals were synchronised to those of the motion analyser used for OEP and sent to a personal computer for subsequent analysis. Oxygen saturation was measured by pulse oximetry (Biox 3700e, Ohmeda, Louisville, CO, USA).

Protocol

After performing spirometric and plethysmographic measurements in the body box the subjects were asked to sit on an electrically braked cycle ergometer. Once acclimatised, quiet breathing for 3 minutes and a slow vital capacity to determine chest wall volumes at functional residual capacity (FRC), total lung capacity (TLC), and residual volume (RV) were measured. The patients than began pedalling for 3 min with 10 W increases in workload every subsequent 3 minutes until exhaustion. Data were collected during the last minute of each workload, including the subject's subjective assessment of breathing difficulty and leg fatigue using a 10 point modified Borg category scale.[14] During both rest and exercise the subjects grasped handles positioned at mid-sternum level, which lifted the arms away from the rib cage, so that lateral markers could be visualised.

Data analysis

Modelling of the chest wall

The chest wall was modelled as if it was composed of two compartments—rib cage and abdomen. A change in abdominal volume (Vab) was defined as the volume swept by the abdominal wall and the boundary between the rib cage and abdomen along the lower costal margin anteriorly and at the level of the lowest point of the lower costal margin posteriorly. Total chest wall volume (Vcw) equalled the sum of rib cage volume (Vrc) and Vab. The pulmonary and abdominal rib cage compartments have been combined as Vrc in this analysis.

Comparison between chest wall and pneumotachographic volumes

As in previous studies in which we assessed the ability of OEP to measure changes in lung volume,[5 7 9 10] we compared changes in Vcw during inspiration obtained by OEP (ΔVcw) with inspired volumes obtained by integration of flow (ΔVm), considering the difference between values at the beginning and end of inspiration. For each instrumented patient, 5–6 breaths were studied during both quiet breathing and at their maximal workload during exercise. Data were then compared by linear regression analysis.

Chest wall, ventilatory pattern and work of breathing

During quiet breathing and exercise OEP data were used to measure end expiratory and end inspiratory Vrc, Vab, and Vcw and the complete ventilatory pattern (including tidal volume, breathing frequency, minute ventilation, inspiratory and expiratory times) at each workload. All volumes reported are the combined mean values over the last minute of each run (unless otherwise specified). The work of breathing performed on the lung in the instrumented patients was calculated as the area enclosed by the Poes–Vcw loops.

Patients were considered to show dynamic hyperinflation of the chest wall if the end expiratory Vcw increased above its resting value at maximum workload. Those in whom Vcw was maintained or reduced were described as euvolumic. This terminology was the same as that used in other published papers[15 16] in which similar patterns of behaviour were found in healthy subjects in response to an incremental exercise test with expiratory flow limitation artificially induced by a Starling resistor.

Statistical analysis

Data are presented as mean (SE) unless otherwise stated. Differences between anthropometric, spirometric, and exercise data sets were tested using Wilcoxon and Mann-Whitney tests for paired and unpaired data, respectively, with a 5% significance level. To compare chest wall volumes at end expiration and end inspiration at different workloads between euvolumic and hyperinflator patients we applied a repeated measures analysis of variance (ANOVA). This enabled us to test for an overall difference between workloads (within-subject effect) and between groups (euvolumics *v* hyperinflators). When ANOVA was significant, post hoc Fisher's PLSD test was performed to verify the statistical significance of the differences between pairs of means. For all tests the significance level was taken as $p<0.05$.

RESULTS

Baseline anthropometric and pulmonary function data are shown in table 1. Instrumentation did not influence exercise performance or the changes in Vcw during exercise.

Comparison of OEP with pneumotachograph data

The relationship between ΔVcw (OEP) and ΔVm (pneumotachograph) is shown in fig 1. Each data point represents the mean of 10–15 breaths either during quiet breathing or at maximum exercise. The linear regression analysis provided the following equation: $\Delta Vcw = 1.12 \cdot \Delta Vm - 0.08$ ($r^2 = 0.92$, $p<0.0001$). Using the same data, the mean (SE) percentage difference between ΔVm and ΔVcw (computed as $(\Delta Vm - \Delta Vcw)/\Delta Vm \times 100$) was −4.3 (2.5)%. When only quiet breathing data were considered the equation was $\Delta Vcw = 1.16 \cdot \Delta Vm + 0.17$ ($r^2 = 0.933$, $p<0.001$) with a mean (SE) percentage difference of 0.8 (3.2)%; when only exercise data were considered the equation was $\Delta Vcw = 0.95 \cdot \Delta Vm - 0.15$ ($r^2 = 0.92$, $p<0.001$) with a mean (SE) percentage difference of −9.5 (2.9)%. At rest ΔVm and ΔVcw differed by 5 (30) ml, while at maximum workload the difference was −100 (29) ml, the ΔVcw values being larger.

Changes in end expiratory chest wall volume during exercise

Two patterns of change in Vcw occurred during exercise. End expiratory Vcw increased by a mean (SE) of 592 (80) ml in 12 patients (five instrumented) and decreased in eight others (three instrumented; fig 2, right hand panels). End expiratory Vrc increased significantly by 494 (90) ml in the hyperinflated patients compared with 46 (148) ml in the euvolumic group ($p<0.05$) during unloaded cycling and remained constant thereafter. End expiratory Vab remained constant in hyperinflators throughout exercise with the end inspiratory volumes rising to accommodate the increases in Vrc (fig 2, left hand and middle panels). In euvolumic patients the end expiratory Vab was reduced at the onset of exercise and remained constant thereafter. The right hand panel of fig 2 shows that the change in Vcw (that is, the tidal volume) in these patients was almost entirely the result of the decrease in Vab while end inspiratory Vcw remained almost constant. In contrast, in the hyperinflators end inspiratory Vcw approached the TLC values measured before exercise and this was accomplished by increases in both Vrc and Vab.

Resting lung volumes including IC were not significantly different between the exercise groups nor was the degree of oxygen desaturation during exercise. Both hyperinflator and euvolumic patients reported a similar degree of breathlessness and leg effort scored at peak exercise. However, euvolumic patients had significantly higher BMI, pre-exercise FEV_1, FEV_1/FVC ratio, and forced expiratory flows at 25% and 50% of expired volume (table 1).

Flow, pressure, and regional volume relationships

Figure 3 shows the flow-volume and compartmental pressure-volume relationships of two representative subjects, one hyperinflator (top panels) and one euvolumic (bottom panels). The hyperinflator had a rightward displacement of the tidal flow-volume loop at peak exercise with an expiratory flow profile that had changed little from that under resting conditions. There was an increase in both rib cage and abdominal volumes with little change in the shape of the pressure-volume loop. In contrast, in the euvolumic patient the expiratory flow was increased during exercise at close to the resting end expiratory volume with marked abdominal muscle pressure generation. This pattern was consistent in all the patients in which it could be assessed.

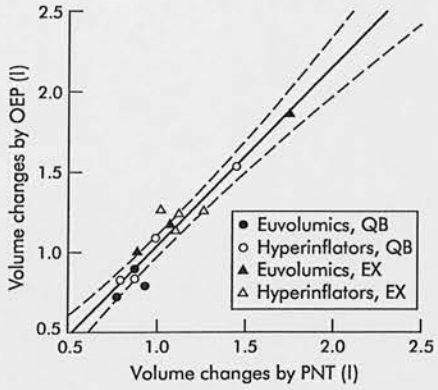

Figure 1 Comparison of the simultaneously recorded integrated flow at the mouth (measured by pneumotachograph, PNT) and change in Vcw (measured by optoelectronic plethysmography, OEP) during quiet breathing (QB) at rest and at maximum workload during exercise (EX) in euvolumic patients (closed symbols) and hyperinflators (open symbols). Each point represents the mean value for each individual. The solid line is the slope of the regression between the data sets and the dashed lines are the 95% confidence intervals. The slope of the regression line (equal to 1.12) reflects the combined effect of gas compression, blood displacements away from the thorax, and the difference in thermodynamic conditions (ATPS *v* BTPS).

Exercise capacity, breathing pattern, and respiratory pressures

Although peak exercise ventilation was the same, hyperinflators reached a mean (SE) maximum workload of 35.0 (4.8) watts with an exercise duration of 13.7 (1.4) min, while the euvolumic patients achieved a maximum workload of 20.0 (4.2) watts and an exercise duration of 8.8 (1.3) min ($p<0.05$). The change in end expiratory Vcw was weakly related to the maximum workload achieved ($r^2 = 0.216$, $p = 0.038$; fig 4).

Tidal volume and frequency at maximum workload were similar in the two groups with no significant difference in the

Table 1 Mean (SD) baseline anthropometric and pulmonary function data of study subjects and subgroups defined by their end expiratory lung volumes during exercise

	All (n = 20)	Euvolumics (n = 12)	Hyperinflators (n = 8)
Age (years)	68.6 (7.0)	65.2 (8.5)	70.9 (5.0)
BMI (kg/m²)	25.5 (2.8)	27.5 (3.0)	24.2 (1.7)*
FEV_1 (l)	1.28 (0.38)	1.42 (0.43)	1.18 (0.33)
FEV_1 (% pred)	43.6 (11.6)	50.1 (12.2)	39.2 (9.2)*
FVC (% pred)	73.5 (16.3)	75.7 (9.8)	72.1 (19.9)
FEV_1/FVC (%)	46.0 (8.4)	51.4 (8.5)	42.5 (6.3)*
IC (l)	2.35 (0.44)	2.18 (0.21)	2.46 (0.53)
TLC (% pred)	128.7 (18.7)	134.0 (34.1)	125.7 (18.7)
FRC	174.2 (44.1)	177.6 (58.6)	172.2 (36.0)
RV (% pred)	202.9 (59.6)	210.3 (78.8)	198.6 (48.7)
$FEF_{25\%}$ (% pred)	19.1 (10.8)	25.2 (14.5)	15.1 (4.7)*
$FEF_{50\%}$ (% pred)	14.8 (7.0)	19.0 (9.0)	12.1 (3.5)*
$FEF_{75\%}$ (% pred)	17.6 (5.8)	18.5 (7.1)	17.0 (5.1)

*$p<0.05$, hyperinflators *v* euvolumics.

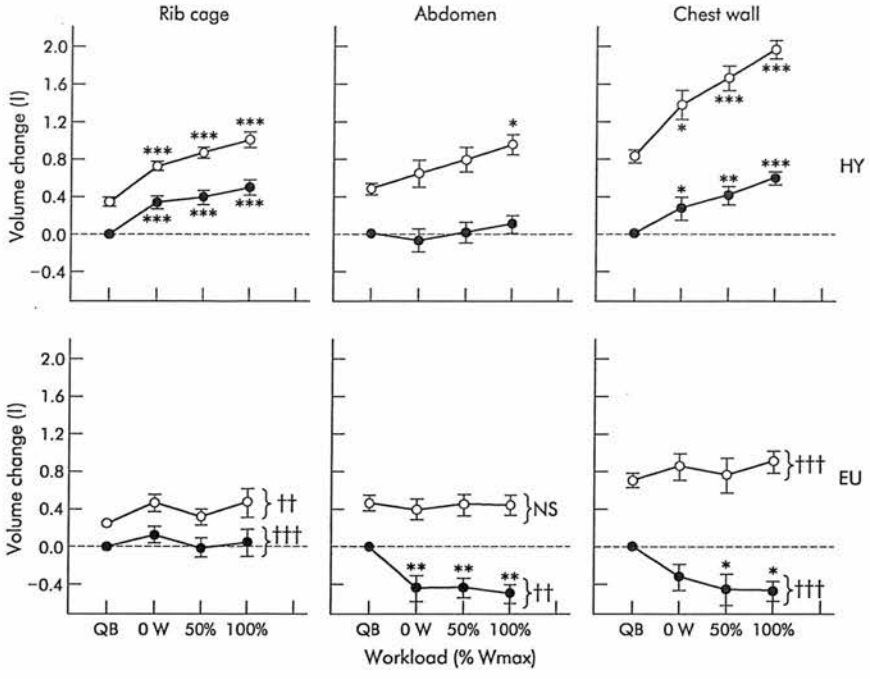

Figure 2 Compartmental and total chest wall volume changes in hyperinflating (upper panels, HY) and euvolumic (lower panels, EU) patients. Open circles = end inspiration; closed circles = end expiration. Mean values and standard error bars are shown. *p<0.05, **p<0.01, ***p<0.001 *v* quiet breathing (QB); †p<0.05, ††p<0.01, †††p<0.001 hyperinflators (HY) *v* euvolumics (EU).

inspiratory or expiratory times between the subgroups (table 2).

In the instrumented patients the mean and peak transdiaphragmatic pressure swings remained relatively constant at rest and during exercise. The mean abdominal pressure swings at maximum exercise were negative in both groups and the maximal abdominal pressures were three times greater in the euvolumics than in the hyperinflators, but the difference was not statistically significant (table 2).

Although resting and peak exercise oxygen consumption were similar in both groups, the calculated work of breathing at the same level of exercise was substantially greater in the euvolumic patients ($p<0.05$).

DISCUSSION

When healthy subjects exercise, end expiratory lung volume falls as ventilation increases—a change seen in young adults[8] and in healthy elderly subjects of a similar age to our patients.[17] Changes in lung volume can be inferred from changes in IC, but the respiratory response to exercise also involves the distribution of these volume changes to different chest wall compartments involving the activity of different groups of respiratory muscles. Initial studies of Vcw in patients with COPD used semi-quantitative methods based on magnetometers and were the first to show that dynamic hyperinflation occurred during exercise in some of these patients.[3 18] OEP represents an important technical advance which has allowed us to define how Vcw changes during exercise in patients with COPD. As a result, we have identified two different behaviour patterns in changes to end expiratory Vcw during exercise.

Studies with externally applied flow resistance in healthy subjects showed differences in the pattern of response to exercise, with some maintaining the normal fall in EELV throughout exercise while others allowed EELV to rise before stopping.[15] In most of our COPD patients end expiratory Vcw increased with exercise, but in a significant number the pattern seen in healthy subjects was adopted with reduced Vab preventing dynamic hyperinflation. In each case the response of a particular individual was constant and the differences between groups at each workload were statistically significant (fig 2). The hyperinflators reached end inspiratory volumes close to their resting TLC while the euvolumic patients had an apparent end inspiratory reserve when they stopped. The change in end expiratory Vrc occurred in hyperinflators before loaded exercise began—a finding previously noted in COPD patients using less quantitative methods[18 19]—and it did not change further in either group as exercise intensity increased. The effect of exercise on the abdominal compartment was equally distinct with end inspiratory Vab increasing in hyperinflators, while in euvolumic patients the end inspiratory Vab remained constant but higher abdominal pressure developed to try to reduce end expiratory Vab (fig 3).

It is not clear why these different responses to exercise occur. The presence of balloon catheters or breathing via a mouthpiece did not explain the pattern observed. All patients had omitted their normal bronchodilator drugs and none had undergone pulmonary rehabilitation, an intervention which can modify changes in lung volume during exercise.[20] There was no difference in the oxygen saturation during exercise and the oxygen consumption, when measured, was similar at equivalent workloads. Although the BMI differed between the groups, this is likely to reflect differences in disease severity, with euvolumic patients having significantly better spirometric parameters. Differences in the relative amounts of emphysema or small airways disease might be relevant, although the presence of emphysema is not necessary for dynamic hyperinflation to occur.[21]

The most likely explanation is a difference between groups in their resting expiratory flow reserve. The hyperinflators reported here are very similar to those reported by O'Donnell and colleagues,[21] exhibiting quantitatively similar changes in end expiratory Vcw using optoelectronic measurement to

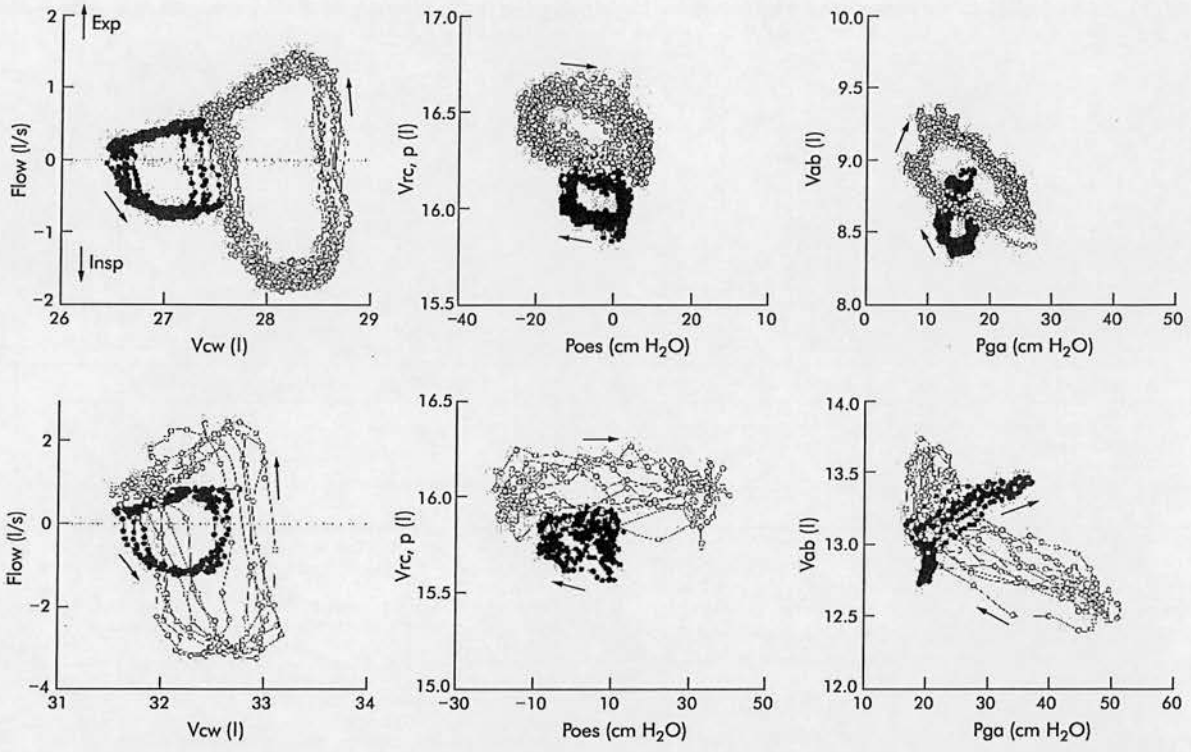

Figure 3 Relationships between tidal flow, chest wall volumes, and pressures in two representative patients, one hyperinflator (top panels) and one euvolumic (bottom panels). The data represent the composite values during sequential breaths at specific flow, volume and pressure. Solid symbols are values measured at rest and open symbols are those measured at maximal exercise. In the left hand panels flow at the mouth is related to chest wall volume (Vcw). The tidal loops of the hyperinflating patient are displaced rightward during maximal exercise while in the euvolumic patient tidal expiratory flow is increased without a substantial increase in end expiratory lung volume (EELV). In the middle two panels the volume of the pulmonary rib cage (Vrc,p) is related to oesophageal pressure (Poes). These data have been selected as only the pulmonary rib cage is exposed to pleural pressure.[8] In both patients there is an increase in end inspiratory and end expiratory pulmonary Vrc at maximal exercise compared with rest, although significantly higher end expiratory Poes values were seen in the euvolumic patient. In the right hand panel abdominal volume (Vab) is plotted against gastric pressure (Pga). With exercise there is little change in the pressure-volume loop of the hyperinflating patient, but a marked shift in the axis of the loop occurred in the euvolumic patient which suggests a strong recruitment of expiratory muscles acting on this compartment.

those in EELV measured using the IC technique and with similar impairments in resting spirometry and expiratory flow. Data from the composite tidal flow-volume loops in our patients are compatible with the presence of resting tidal flow limitation which is associated with hyperinflation in COPD.[22] In contrast, the euvolumic patients were less obstructed and had less marked flow limitation at lung volumes within the resting tidal range, as assessed by their maximum pre-exercise flow-volume loops and the non-invasive data shown in fig 3. Despite their better inspiratory flow reserve, euvolumic patients developed high intra-abdominal pressure rather than permitting EELV to rise as in the hyperinflators.

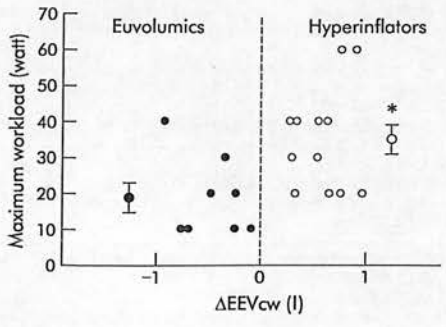

Figure 4 Relationship between change in end expiratory chest wall volume from quiet breathing to exercise (ΔEEVcw) and maximum exercise workload reached by euvolumic and hyperinflator patients. Mean values and standard error bars are shown for the two groups; *p<0.05.

Whatever the explanation, maintaining a normal end expiratory lung volume is a poor adaptive strategy. The calculated work of breathing at end exercise was substantially higher in the euvolumic patients than in the hyperinflators, confirming that exercise was not limited by poor motivation in this group. The increase in oxygen consumption by the respiratory muscles in euvolumic patients resulting from this increase in work of breathing effectively competes for a larger share of the whole body oxygen consumption, reducing the oxygen available to the leg muscles.[23–25] This may explain why patients who adopted this strategy, although as breathless as hyperinflators when they stopped, exercised for less time and reached a lower intensity of power at equivalent levels of breathlessness.

Measurements of Vcw are normally identical to the volume change recorded at the mouth during spontaneous breathing[5 7 10] or that measured in ventilated and paralysed patients.[11] In our COPD patients there was good overall agreement between the inspiratory tidal volume and Vcw, amounting to an error of 0.8% at rest, equivalent to a difference of 5 ml in the resting tidal volume. This increased to a 9.5% error at maximal exercise, equivalent to a difference

Table 2 Mean (SE) values of exercise performance, breathing pattern, exercise duration, respiratory pressures, energetics and sensation at rest and maximal exercise (Wmax) for the euvolumic and hyperinflating subjects

	All		Euvolumics		Hyperinflators	
	Rest	Wmax	Rest	Wmax	Rest	Wmax
Exercise duration (min)	11.8 (1.0)		8.8 (1.3)		13.7 (1.4)*	
Wmax (watt)	29.0 (3.4)		20.0 (4.2)		35.0 (4.8)*	
Breathing frequency (/min)	16.8 (1.0)	27.3 (1.6)	18.5 (1.0)	26.9 (3.1)	15.59 (1.49)	27.51 (1.69)
Ti (s)	1.47 (0.11)	0.91 (0.06)	1.27 (0.06)	0.94 (0.10)	1.61 (0.20)	0.90 (0.07)
Te (s)	2.41 (0.18)	1.49 (0.15)	2.03 (0.13)	1.62 (0.35)	2.67 (0.32)	1.40 (0.14)
Minute ventilation (l/min)	12.7 (1.0)	37.1 (2.5)	12.7 (0.9)	35.9 (4.2)	12.6 (1.6)	37.9 (3.2)
Maximum Ppl (cm H_2O)	3.5 (1.4)	14.0 (4.6)	4.4 (2.9)	22.6 (8.5)	2.7 (1.5)	6.8 (3.4)
Maximum Pab (cm H_2O)	5.8 (1.7)	14.2 (4.6)	6.7 (3.7)	22.1 (9.0)	5.1 (2.0)	7.6 (2.6)
Work of breathing (cm H_2O·l/min)	140 (31)	456 (132)†	155 (12)	754 (228)†	130 (47)	277 (77)*†
Oxygen consumption (ml/min)	259 (14)	558 (20)†	248 (10)	539 (29)†	267 (25)	570 (29)†
Heart rate (bpm)	86 (5)	104 (3)	95 (6)	102 (6)	80 (6)	105 (3)
Breathlessness	0.8 (0.3)	4.8 (0.5)	1.1 (0.5)	4.9 (0.9)	0.6 (0.3)	4.8 (0.5)
Leg effort	1.6 (0.5)	5.6 (0.5)	3.1 (0.6)	6.6 (0.8)	0.6 (0.3)*	4.9 (0.5)

To permit comparison between different subjects, Pga data are presented as abdominal pressures (Pab) by subtracting the hydrostatic pressure gradient.
*$p<0.05$, hyperinflators *v* euvolumics.
†10 watt.

of 100 ml in the mean tidal volume. This difference is likely to arise from physiological rather than methodological factors. The change in Vcw tended to be larger than the volume change at the mouth and was more marked during expiration, reflecting the effect of gas compression and also the shift of blood between thoracic and extrathoracic regions.[15]

Our data have clinical implications. They help explain why spirometry is such a poor predictor of exercise capacity in individual COPD patients, since those with apparently better resting values can still be limited by their efforts to reduce end expiratory Vcw. Evidence from studies at rest in patients with COPD and with kyphoscoliosis[26] suggest that the order of recruitment of the respiratory muscles during breathing is an automatic response of the central controller. This stereotyped behaviour may explain why some patients with COPD adopt a euvolumic breathing pattern during exercise. Whether previously euvolumic patients adapt to the onset of persistent tidal flow limitation and then allow Vcw to rise remains to be established. Some therapeutic interventions may work by modifying these volume related exercise responses. Thus, in healthy subjects, reducing the work of breathing can increase the oxygen consumption of the locomotor muscles,[24 25] while in patients with COPD the major effect of supporting ventilation during exercise is to increase exercise duration in patients with the most marked abdominal muscle activation.[27]

In conclusion, exercise limitation in COPD and its attendant dyspnoea is not necessarily associated with dynamic pulmonary hyperinflation. Individuals vary in the strategy of respiratory muscle recruitment that they adopt and in the resultant change in compartmental chest wall volume. The reasons for this require further investigation, and the OEP technique may be helpful in understanding the effects of treatment on exercise performance in COPD.

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LUNG ALERT

Interferon gamma therapy and pulmonary fibrosis

▲ Raghu G, Brown KK, Bradford WZ, *et al.* A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004;**350**:125–33

In this double blind multinational study, 330 patients with idiopathic pulmonary fibrosis were randomly assigned to treatment with either subcutaneous interferon gamma-1b (n = 162) or placebo (n = 168) three times daily for 48 weeks. Interferon gamma-1b had no significant effect on the primary end point (disease progression or death) compared with placebo. 10% of patients died in the active treatment group compared with 17% in the placebo group (p = 0.08). The median time to death or disease progression was 439 days in the active group and 344 days in the placebo group (p = 0.50). Active treatment was not associated with any differences in gas exchange, lung function, or conventional quality of life measures. Exploratory analysis did reveal a greater effect of the active treatment in reducing mortality in patients with milder disease (parameter > median value of the group—that is, baseline forced vital capacity (FVC) >62% predicted and carbon monoxide transfer factor >35% predicted). Active treatment was associated with more frequent influenza-like symptoms and a higher incidence of pneumonia. However, respiratory infections were of equal severity and discontinuation rates were similar in the two groups.

This study failed to show any significant effect of interferon gamma-1b on disease progression, death, gas exchange, lung function, or quality of life in idiopathic pulmonary fibrosis. Exploratory analysis suggested, but could not confirm, a survival benefit for the active treatment in patients with milder disease. Due to the limited size and duration of the trial, a smaller survival benefit cannot be excluded. Further trials are required of adequate power to answer these questions.

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Antiretroviral therapy improves outcome of HIV infected adults with TB

▲ Hung CC, Chen MY, Hsiao CF, *et al.* Improved outcomes of HIV-1-infected adults with tuberculosis in the era of highly active antiretroviral therapy. *AIDS* 2003;**17**:2615–22

In this prospective observational cohort study from Taiwan the outcome of HIV infected TB patients and HIV infected non-TB patients treated with highly active antiretroviral therapy (HAART) was compared.

A total of 46 TB and 230 non-TB antiretroviral naive patients were included between June 1994 and October 2002. The median duration of antituberculous therapy was 9 months (range 1–24). Viral clearance (20 of 46 *v* 107 of 230, RR 0.93 (95% CI 0.65 to 1.34); p = 0.71) at week 4 of HAART was similar in the two groups, as was the virological failure during HAART (RR 1.49 (95% CI 0.92 to 2.41); p = 0.14). The CD4 cell count increased in both groups (71 *v* 64 $\times$ 10^6 cells/l, p = 0.70). The risk for HIV progression to new opportunistic illnesses (adjusted RR 1.16 (95% CI 0.764 to 1.77)) and the adjusted hazard ratio for death of TB patients compared with non-TB patients was also similar in the two groups (1.18 (95% CI 0.65 to 2.32) before HAART era and 0.89 (95% CI 0.57 to 1.69) in HAART era).

This study addresses the important issue of HIV and TB co-infection and shows that TB does not alter the virological and immunological responses and the clinical outcome when these patients are treated with HAART and an appropriate antituberculous therapy. The authors do point out, however, that the rate of multidrug resistant TB was low and few of these patients were intravenous drug users or homeless, distinguishing them from some other study populations. They had access to high quality follow up and treatment. Ideally, we would like to have a situation where we could provide care of an equally high standard to all patients with HIV and TB co-infection to ensure that these results are widely applicable.

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Regional chest wall volumes during exercise in chronic obstructive pulmonary disease

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Paradoxical movement of the lower ribcage at rest and during exercise in COPD patients

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ABSTRACT: Paradoxical inward displacement of the costal margin during inspiration is observed in many chronic obstructive pulmonary disease patients at rest but its importance is unclear.

The current authors studied 20 patients (forced expiratory volume in one second 32.6±11.7, functional residual capacity 186±32% predicted) and 10 healthy controls at rest and during symptom-limited incremental exercise. With optoelectronic plethysmography, the phase shift between pulmonary and abdominal ribcage volumes and the percentage of inspiratory time the ribcage compartments moved in opposite directions were quantified, using control data to define the normal range of movement.

Eight patients showed lower ribcage inspiratory paradox at rest (P+), while 12 patients did not (P-). This was unrelated to resting lung function or exercise tolerance. Total end-expiratory chest wall volume (EEV_{CW}) increased immediately when exercise began in P+ patients, but later in exercise in P- patients. This difference in EEV_{CW} was mainly due to a greater increase of end-expiratory pulmonary ribcage volume in P+ patients. During exercise, dyspnoea increased similarly in the two groups, while leg effort increased more markedly in the patients without paradox.

In conclusion, lower ribcage paradox at rest is reproducible and associated with early-onset hyperinflation of the chest wall and predominant dyspnoea at end-exercise. When paradox is absent, the sense of leg effort becomes a more important symptom limiting exercise.

KEYWORDS: Chest wall asynchrony, chronic obstructive pulmonary disease, dyspnoea, exercise, Hoover's sign

In healthy people, inspiration occurs as a result of the coordinated action of the chest wall muscles. As the diaphragm flattens, the incompressible abdominal contents displace the abdominal wall outwards. The ribcage comprises two linked compartments: the lung-apposed part (pulmonary ribcage (RC_P)), expanded by inspiratory ribcage muscle action and submitted to pleural pressure; and the diaphragm-apposed part (abdominal ribcage (RC_A)), expanded as this muscle contracts and submitted to abdominal pressure. During inspiration, the expansions of the abdomen and both ribcage compartments are in phase, a relationship that persists when the subject exercises although end-expiratory lung volume is actively reduced by increased expiratory abdominal muscle action [1].

In chronic obstructive pulmonary disease (COPD) the situation is different. Here, the diaphragm is flatter and the respiratory drive is increased [2]. In this condition, the effectiveness of the diaphragm is less than in normal subjects and the expansion of the lower ribcage caused by diaphragmatic contraction is smaller than in normal subjects; consequently, it is possible that an uncoordinated expansion of the two ribcage compartments occurs, leading to ribcage distortion [3, 4]. Before the advent of objective measurements of chest wall volume, clinical observation had identified patients who exhibited paradoxical (inward) movement of their lower ribcage on inspiration [5–8]. Such inspiratory paradoxical motion of the lower ribcage is common in COPD [7, 8] and has been proposed

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as an aid to diagnosis [9]. However, it has not been quantified or related to other forms of respiratory behaviour or the symptoms which limit exercise.

Previously, optoelectronic plethysmography (OEP) has been used to identify differences in the behaviour of the ribcage and abdominal compartments of COPD patients during rest and exercise [10–13]. However, the effect of within-breath asynchrony between different ribcage compartments was not studied. The current authors hypothesised that the presence of lower ribcage paradoxical movement would relate to the pattern of the end-expiratory and end-inspiratory chest wall volume changes during exercise. To test this, the normal range of lower ribcage paradox was defined by studying a group of age-matched healthy controls, and then regional chest wall volumes at rest and during exercise in stable COPD were measured. Additionally, to investigate the relevance of paradoxical lower ribcage movement to exercise undertaken in daily life, exercise performance and symptoms during self-paced corridor walking were measured.

METHODS

Subjects

In total, 20 male patients who met the clinical and physiological diagnostic criteria for COPD [14] were studied. All patients were or had been tobacco smokers, were <75 yrs old and had a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.7, a pre-bronchodilator FEV_1 <50% predicted and showed <10% improvement in FEV_1 after inhaled bronchodilator drugs. Patients were not known to have paradoxical lower ribcage movement prior to the study and no specific examination for the presence of Hoover's sign [5, 6] was undertaken. No patient had experienced a COPD exacerbation requiring treatment in the previous 6 weeks. All were treated with inhaled corticosteroids and long-acting inhaled bronchodilators together with short-acting rescue therapy. In addition, 10 healthy age-matched volunteers were recruited, who followed the same measurement protocol as follows. Subjects had normal spirometry for their age and an FEV_1/FVC value >0.7.

Protocol

All assessments were made on a single study day. After clinical review, spirometry and plethysmographic lung volumes were measured in all subjects and repeated in the COPD patients 15 min after 400 μg salbutamol given *via* a spacer device. Each COPD patient performed two 6-min walking tests with a 20-min rest period between testing. The first walk was used to familiarise the patient with the test and only data from the second walk are reported. After a 20-mins rest, during which the OEP reflective markers were applied, patients were seated on the cycle ergometer and asked to execute three slow vital capacity and three FVC manoeuvres followed by 2 min of quiet breathing (QB), to establish baseline values for the chest wall volumes. After this, subjects undertook the incremental exercise protocol described hereafter. Subject started pedalling, first unloaded for 2 min and then with an incremental load of 5 $W \cdot min^{-1}$ until exhaustion.

The research protocol was approved by the district research ethics committee (Liverpool, UK) and informed consent was obtained from each participant.

Measurements

Subdivisions of lung volumes were measured to American Thoracic Society (ATS) standards in a body plethysmograph (Medgraphic Autolink 1085D; Medical Graphics, St Paul, MN, USA). Flow was measured at the mouth by a screen pneumotachograph and integrated to display the flow–volume loop from which spirometry and flow indices were derived.

Self-paced corridor walking tests were performed according to standard protocols with a standardised walking course [15]. Subjects walked at their maximal pace along an elliptical 40-m course. They were asked to cover as much ground as possible during the allotted time, while maintaining a steady pace without running. No encouragement was given, and subjects were informed each minute of the time remaining. The patients were allowed to stop, but they could start again, if possible, within the allocated 6 min. Distance covered in 6 min was recorded, together with oxygen saturation and heart rate (HR) from a lightweight pulse oximeter (Pulsox 300i; Konica Minolta Sensing, Inc., Osaka, Japan). During exercise, subjects were asked to rate their breathlessness and the sense of leg effort every minute on a 10-point modified Borg category scale.

Incremental exercise was performed while seated on an electrically braked cycle ergometer. With the subjects breathing through a mouthpiece with a nose-clip, breath-by-breath ventilatory variables were derived from the flow signal detected by a pneumotachograph system (Medical Graphics). Oxygen consumption and carbon dioxide production were measured using a paramagnetic sensor and infrared carbon dioxide analyser, respectively, as part of an exercise testing system (Medical Graphics). The flow signal was synchronised to that of the motion analyser used for OEP and sent to a personal computer for subsequent analysis. Oxygen saturation was measured by pulse oximetry (Biox 3700e; Ohmeda, Louisville, CO, USA) and cardiac frequency was determined using the R-R interval from a 4-lead ECG. During the exercise tests, subjects were asked to rate their breathlessness and leg effort every minute on the same Borg category scale used in the walking tests.

Kinematics of the chest wall were measured by OEP (OEP System; BTS, Milan, Italy). In brief, the volumes displaced by the three compartments of the chest wall were measured by 89 retro-reflective markers placed on the trunk of the subject according to precise anatomical reference points. Marker positions were captured by six TV cameras (three in front and three behind the subject) operating at 60 $frames \cdot s^{-1}$ and synchronised with co-axial infrared flashing LEDs. The three-dimensional coordinates of the markers were calculated with stereo-photogrammetry and linked with a mesh of triangles to create the surface embedding the trunk. The volume of the trunk enclosed by the surface was obtained through a computing algorithm based on the Gauss' theorem [16].

The markers (fig. 1) were positioned on approximately horizontal rows at the following levels: the clavicular line, the manubrio-sternal joint (angle of Louis), the nipples, the xiphoid process, the lower costal margin, the umbilicus and the anterior superior iliac crest. Surface landmarks for the vertical columns were: the midlines, both anterior and posterior axillary lines, the midpoint of the interval between the midline and the anterior axillary line, the midpoint of the interval between the midline

and the posterior axillary line, and the midaxillary lines. Extra markers were added bilaterally at the midpoint between the xiphoid and the most lateral portion of the 10th rib, in the region overlying the lung-apposed ribcage, and in corresponding posterior positions. Volume displacement of the chest wall was calculated by triangulating the surface and integrating the subtended volume.

Data analysis

Modelling of the chest wall

The chest wall was modelled in three compartments: RC_P, RC_a and abdomen (AB; fig. 1). Thus, the total volume (V) displaced by the chest wall (CW) was calculated as the sum of the volumes displaced by the individual compartments. The boundaries between the three portions were represented by a transverse section placed at the level of the xiphoid process (between RC_P and RC_a) and another surface positioned at the level of the lower costal margin (between RC_a and AB; fig. 1). The time-courses of the volume of each region (V_{RCP}, V_{RCa} and V_{ab}), along with their sum (V_{CW}) was processed to obtain a breath-by-breath assessment of both ventilatory pattern and operational chest wall volumes [1, 4, 16].

Chest wall volume data were standardised for the duration of each test to allow comparisons between different subjects as a percentage of maximum exercise. Comparisons were also made using minute ventilation as a percentage of the maximum value reached and as an absolute value.

Quantitative analysis of the paradoxical movement of the lower ribcage

The presence of paradoxical lower ribcage motion was established by comparing the time-courses of V_{RCP} and V_{RCa}. In each patient, the volume tracings were normalised with respect to time, in order to allow ensemble averaging over three reproducible consecutive breaths randomly chosen within the period of interest (either QB or during exercise at different levels) and to derive an "average" respiratory cycle at each level of workload. Inspiratory and expiratory phases of the breathing cycles were derived from the V_{CW} signal. From these average breaths, asynchronous and paradoxical motion between the two ribcage compartments were then assessed by calculating the following two parameters (fig. 2).

First, the phase shift (θ) between V_{RCa} and V_{RCP}, as indicated by the degree of opening of the Lissajou figure produced when these two volumes were plotted against each other, was calculated. This was measured as the ratio of the distance delimited by the intercepts of the V_{RCP} *versus* V_{RCa} dynamic loop on a line parallel to the x-axis at 50% of RC_P tidal volume (m), divided by RC_a tidal volume (s), as $\theta=\sin^{-1}(m \cdot s^{-1})$, an approach previously adopted [17]. In this system a phase angle of zero represents completely synchronous movement of the compartments and 180° total asynchrony.

Secondly, inspiratory paradox time (IP), defined as the fraction of the inspiratory time during which the V_{RCa} decreased (fig. 2), was calculated.

Patients were subdivided into those showing paradox at rest (P+) and those who did not (P-). This grouping was based on threshold values of IP and θ, obtained at rest before the various manoeuvres in the 10 healthy volunteers and defined as values two standard deviations beyond the respective means. To confirm the validity of these measurements, three different breaths were selected under the same workload in both the control and COPD subjects and the data compared with the initial estimate. In three COPD patients, the data on the first incremental test were repeated on a subsequent day to

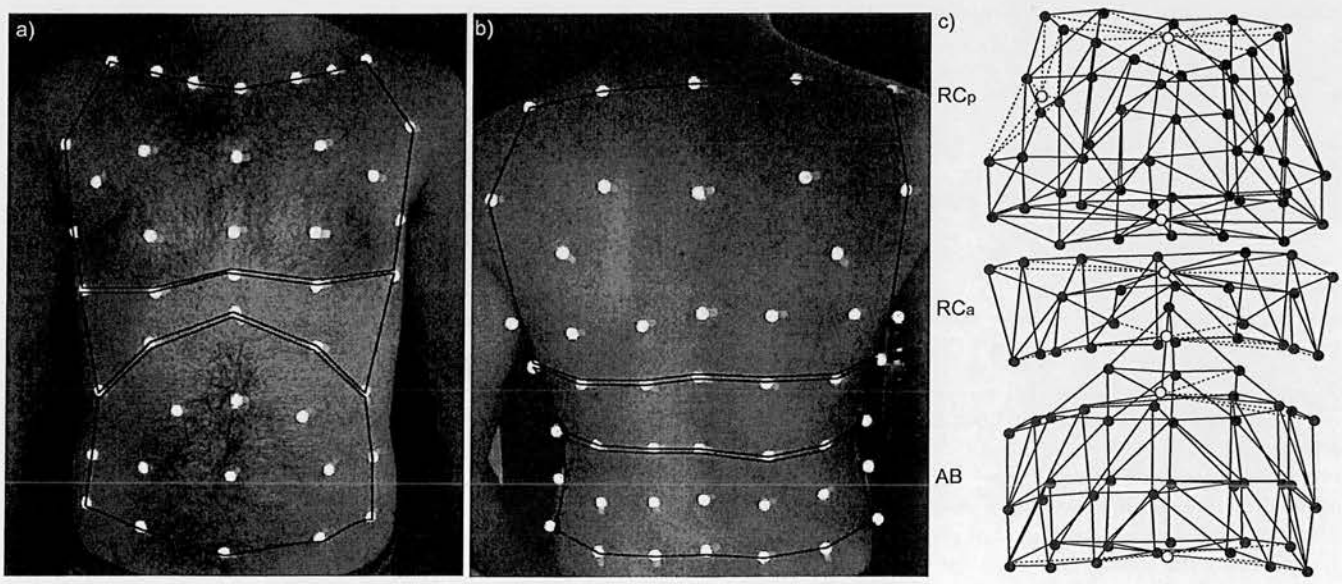

FIGURE 1. Marker positioning on the a) front and b) back of the subject and c) geometrical models of the chest wall compartments for analysis by optoelectronic plethysmography. a and b) Borders of the different compartments of the chest wall are shown: pulmonary or upper ribcage (RC_P), abdominal or lower ribcage (RC_a) and abdomen (AB). c) The actual triangulation for the different compartments of the chest wall (RC_P, RC_a and AB). To allow a better understanding, each compartment is represented slightly shifted in the vertical direction.

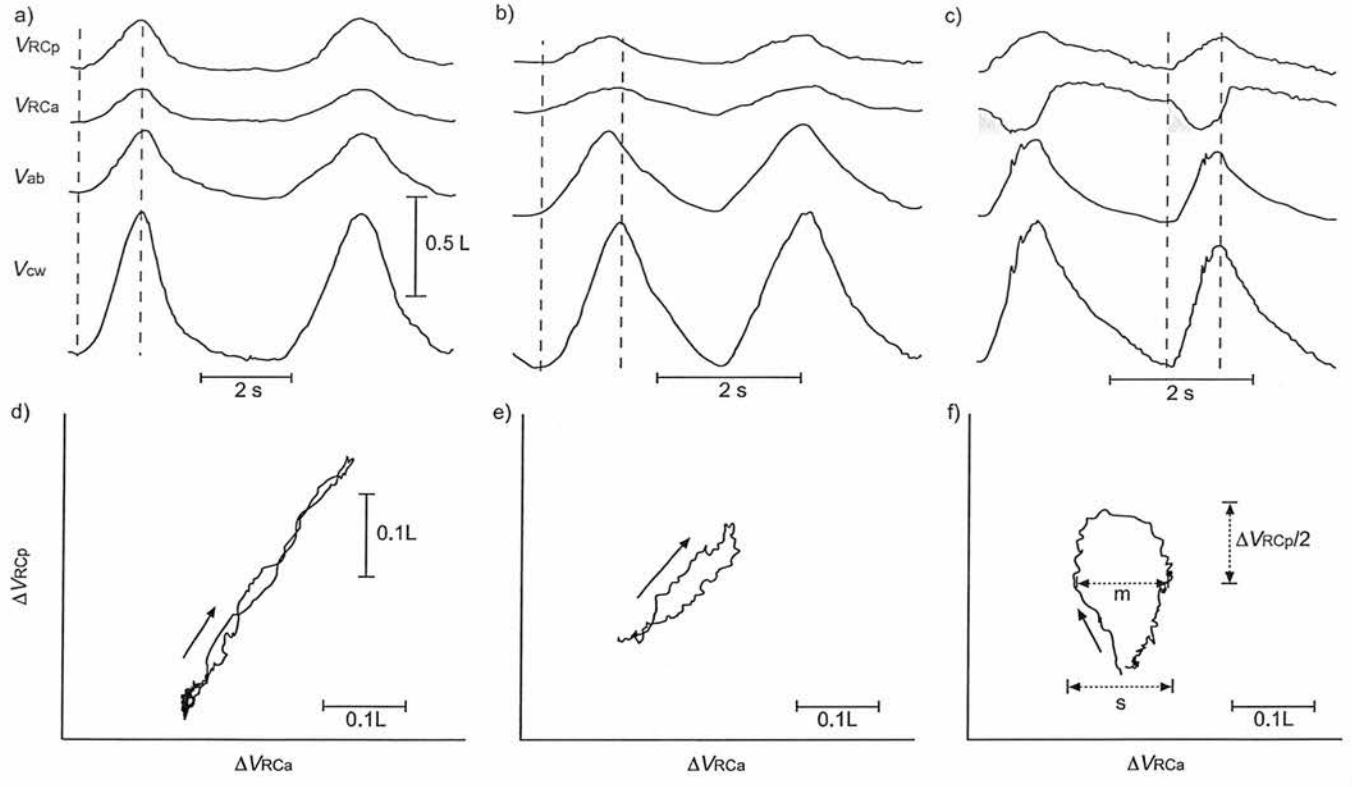

FIGURE 2. a–c) Time-courses of the volumes of the upper ribcage, lower ribcage, abdomen and total chest wall (V_{RCp}, V_{RCa}, V_{ab} and V_{cw}, respectively) during two consecutive breaths at rest. - - - -: boundaries of a single inspiration. d–f) Dynamic loops of change (Δ) in V_{RCp} *versus* ΔV_{RCa} during quiet breathing, averaged on the respiratory cycle time. Arrows: direction of dynamic loops. a and d) Control subject, b and e) chronic obstructive pulmonary disease (COPD) patient without paradoxical movement between V_{RCp} and V_{RCa}, c and f) COPD patient with paradoxical movement between V_{RCp} and V_{RCa}. ▯: inspiratory paradox time of the lower ribcage. m: line parallel to the x-axis at 50% of RCp tidal volume; s: RCa tidal volume. The phase shift is calculated as $\theta=\sin^{-1}(m \cdot s^{-1})$.

determine whether differences in marker position (positioned by different experimenters) or day-to-day variability in the subjects' breathing influenced the classification of paradoxical movement.

As an alternative parameter to θ for the quantification of the degree of opening of the Lissajou figure in the V_{RCp}–V_{RCa} plot, the hysteresivity index (η) was also considered [18]:

$$\eta = ((\pi \cdot \Delta V_{RCp} \cdot \Delta V_{RCa}/4A)^2 - 1)^{-0.5} \quad (1)$$

where ΔV_{RCp} and ΔV_{RCa} are the tidal volumes of the pulmonary and abdominal ribcage, respectively, and A is the area bounded by the V_{RCp}–V_{RCa} loop.

In a *post hoc* analysis, the current authors examined whether the presence of tidal expiratory flow limitation at rest was related to the indices of paradoxical lower ribcage movement and the behaviour of patients during exercise. The flow signal was integrated to obtain flow–volume loops during rest, forced expiratory manoeuvres and maximal exercise. To correct the drift of the volume signal obtained from the integration of the flow measured at the mouth, the loops were positioned according to the values of chest wall volume measured at total lung capacity during inspiratory capacity manoeuvres performed at rest before the various manoeuvres during which the loops to be compared were recorded. Expiratory flow limitation was considered present at rest when >50% of the tidal breath met or exceeded the expiratory boundary of the maximal flow–volume loop [19].

Statistical analysis

Data are presented as mean±SD unless otherwise stated. Differences between anthropometric, spirometric and exercise data sets were tested using Wilcoxon and Mann–Whitney tests for paired and unpaired data, respectively, with appropriate adjustment for multiple comparisons. To evaluate the influence of ribcage paradox and exercise intensity on ventilatory parameters and operational volumes, a two way ANOVA was performed. Statistical significance was assumed if the null-hypothesis was rejected with a probability of $p<0.05$.

RESULTS

Anthropometric characteristics, spirometry values and subdivision of lung volumes are reported in table 1.

Defining the occurrence of paradoxical ribcage movement at rest

The magnitude of volume change, its timing and the phase angle relationship of the RCp and RCa regions are shown for three typical subjects in figure 2, while all the individual V_{RCa} and V_{RCp} time-courses and V_{RCp}–V_{RCa} loops are presented in the online supplementary material. Using a difference of at

TABLE 1 Patient characteristics: anthropometric characteristics, spirometric values and subdivision of lung volumes in chronic obstructive pulmonary disease (COPD) and healthy control subjects

	Control	COPD		
		All	P+	P-
Subjects n	10	20	8	12
Age yrs	65±7	66±7	69±6	65±7
Height cm	173±6	174±6	175±6	173±7
Weight kg	77.0±7	69±14	76±16	63±11*
BMI kg·m^{-2}	25.6±1.6	22.5±3.9	24.6±4.3	21.0±2.9*
FVC L	5.0±1.29	2.9±0.78	2.87±0.77	2.87±0.83
FVC % pred	117.7±29.5	66.0±16.5	65.9±14.4	66.6±17.7
FEV_1 L	3.3±0.5	1.0±0.3	0.9±0.2	1.1±0.4
FEV_1 % pred	102.8±12.7	32.6±11.7	28.0±6.1	35.6±13.6
FEV_1/FVC %	67.0±11.6	36.3±9.4	31.9±5.7	39.3±10.4
FEV_1/FVC % pred	89.9±15.2	48.9±12.6	43.1±7.9	52.7±13.9
TGV L	3.7±0.7	6.5±1.5	6.8±0.7	6.2±1.7
TGV % pred	108.6±20.7	186.4±31.5	189.1±24.1	179.1±34.5
RV L	2.9±0.7	5.6±1.1	5.7±0.7	5.4±1.3
RV % pred	129.9±29.2	239.5±48.9	241.2±35.5	227.9±49.8
TLC L	7.0±0.9	8.6±1.4	8.6±0.9	8.2±1.5
TLC % pred	106.7±11.2	125.7±15.5	126.7±12.2	123.9±16.6
RV/TLC %	40.1±7.4	66.0±7.2	66.0±6.0	65.0±9.1
RV/TLC % pred	124.8±21.3	188.3±15.9	184.3±18.2	194.6±20.5
SVC L	4.2±0.6	3.0±0.7	3.0±0.7	3.0±0.9
SVC % pred	98.4±8.9	68.4±12.1	68.2±11.1	69.8±15.1
IC L	3.3±0.6	1.9±0.4	1.8±0.5	2.03±0.3
IC % pred	103.9±14.7	61.0±12.3	56.6±14.3	64.3±9.9

Data are presented as mean± SD, unless otherwise stated. P+: subjects showing lower ribcage inspiratory paradox at rest; P-: subjects without paradox; BMI: body mass index; FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in one second; TGV: total gas volume; RV: residual volume; TLC: total lung capacity; SVC: slow vital capacity; IC: inspiratory capacity. *: $p<0.05$ for comparison of P+ with P-.

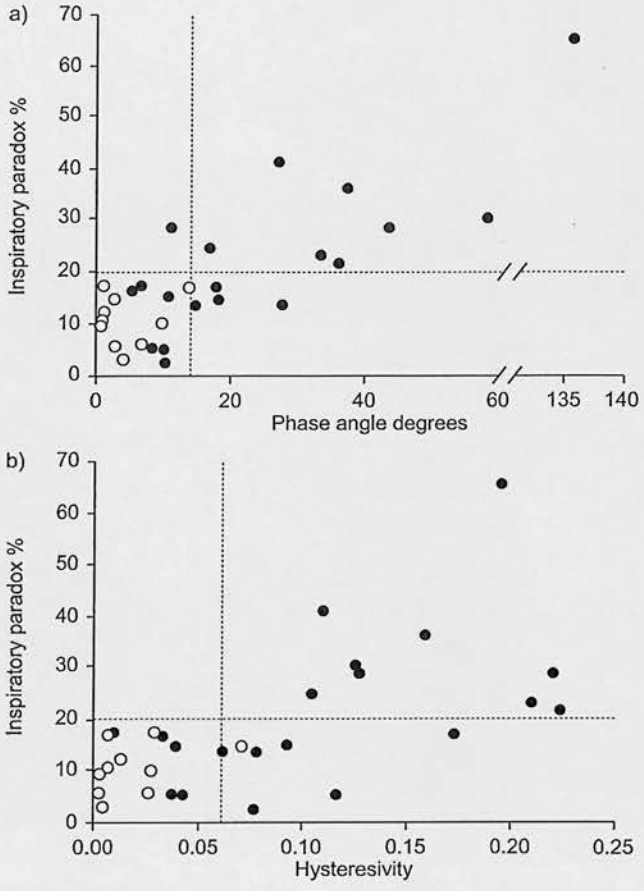

FIGURE 3. a) Relationship between phase of upper *versus* lower ribcage (θ) and inspiratory paradox time (IP) of the lower ribcage. b) Relationship between hysteresivity of upper *versus* lower ribcage (η) and IP of the lower ribcage. ●: chronic obstructive pulmonary disease patients; ○: control subjects. ····: thresholds as defined as two standard deviations beyond the mean values observed in healthy subjects at rest. a) Thresholds θ=14.0° and IP=20.3%, b) thresholds η=0.061 and IP=20.3%.

least two standard deviations above the mean value for the normal subjects (99% confidence interval) gave a threshold for the upper limit of normal of 14.0 degrees for phase angle and 20.3% for the IP. When three different breaths were chosen and the analysis repeated, similar values were obtained and no individual would have been classified as showing ribcage paradox, even if only one criterion were used (see online supplementary material).

Among the COPD patients, eight subjects met both criteria for paradox (P+) while the remaining 12 did not (P-). Of these, seven subjects showed no evidence of paradox by either criteria, four showed only an abnormal phase angle and one an increased IP (fig. 3a).

Both indices of paradoxical lower ribcage movement lay close to the upper limit of normal in the P- subjects but were clearly separate from those in the P+ subjects at rest ($p<0.001$; fig. 4). The reproducibility of the percentage inspiratory time and phase angle in the COPD patient data was good. No patient would have been reclassified had different breaths been chosen. Likewise, no difference was seen among the replicate data on three different occasions both at rest and during exercise (see online supplementary material).

When η was plotted instead of phase angle against IP to investigate ribcage paradox (fig. 3b), among the COPD patients, nine subjects showed values of both IP and η above threshold. Of these, eight subjects were previously classified as P+, and the remaining subject was the one with above-threshold IP and below-threshold θ.

Tidal expiratory flow limitation

Among the P+ patients, all showed clear evidence of expiratory flow limitation at rest using the flow–volume criteria (as aforementioned). Among the P- patients, nine out of the 12 were flow limited and three of these flow-limited patients had a value of phase angle above the threshold (see online supplementary fig. E4).

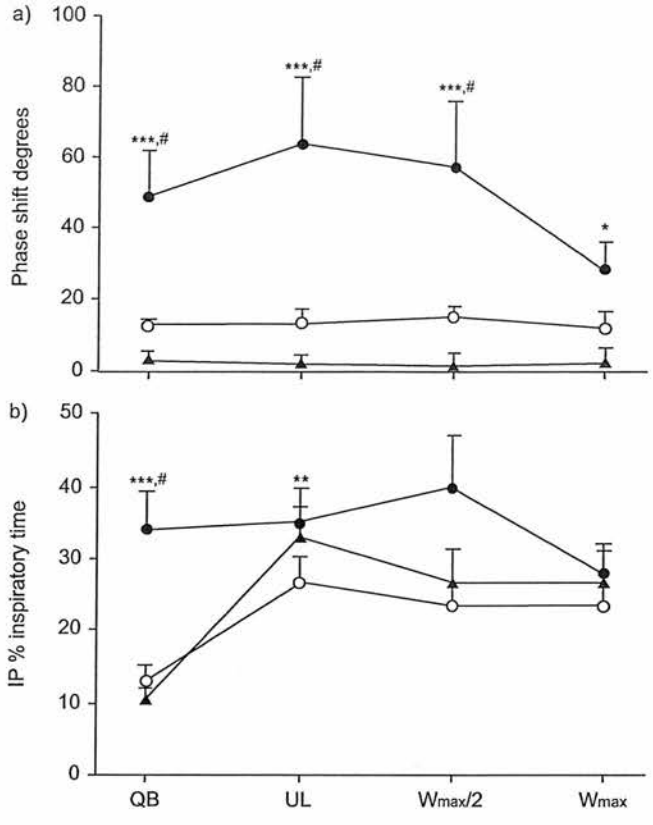

FIGURE 4. Mean±SE of a) phase shifts and b) inspiratory paradox times (IP) during exercise between upper (pulmonary) ribcage and lower (abdominal) ribcage. ●: chronic obstructive pulmonary disease (COPD) subjects showing lower ribcage inspiratory paradox at rest (P+); ○: COPD subjects without paradox (P-); ▲: control subjects. QB: quiet breathing; UL: unloaded exercise; W_{max}: maximum workload exercise. *: $p<0.05$ for comparison of P+ with control; **: $p<0.01$ for comparison of P+ with P-; ***: $p<0.001$ for comparison of P+ with P-; #: $p<0.001$ for comparison of P+ with control.

Paradoxical ribcage movement during exercise

The time-courses of the phase angle and IP during unloaded, half-maximal and maximal exercise are shown in fig. 4. At rest, the P+ group showed, by definition, higher mean phase angle and IP than the P- group. During exercise, the phase angle did not change significantly in the control and the P- groups, but in the P+ group the phase angle fell at maximal exercise so that there was no longer any significant difference between the P+ and the P- groups. The IP patterns, like the phase angle, were similar throughout for the control and P- groups but, unlike the phase angle, increased substantially during exercise, approaching the levels of the P+ group.

Spirometry, lung volumes and exercise performance in COPD

The presence of ribcage paradox was not associated with statistically significant differences in spirometry or any measurement of resting lung volume when compared with patients who did not show this finding. There were no significant differences in the maximum workload, peak oxygen consumption achieved, maximum minute ventilation or breathing pattern between the two groups of COPD patients (table 2).

Chest wall volumes during incremental exercise

None of the control subjects showed evidence of an increased end-expiratory total chest wall volume (EEV_{cw}) at end-exercise relative to their baseline values and all showed an early fall in EEV_{cw} as exercise began (fig. 5). In contrast, P+ subjects showed an early increase in EEV_{cw} (fig. 6a) and this was maintained up to the maximum workload, exceeding the values of the spontaneous breathing by a mean of 328 mL. In contrast, P- subjects maintained an EEV_{cw} similar to the baseline value up to ~50% of maximum workload. EEV_{cw} slowly rose thereafter, showing a late hyperinflation of 297 mL at end-exercise, a value similar to that of the P+ subjects (when volumes were expressed as change from baseline as in figure 6) but statistically different from the healthy volunteers ($p<0.001$). These findings were similar when data where expressed using minute ventilation either as a percentage of the maximum or as an absolute value (fig. 6b).

The time-course of the end-expiratory and end-inspiratory regional chest wall volumes differed significantly between the healthy subjects and the two COPD groups (fig. 7). In P+, RC_P end-expiratory volumes rose immediately after the onset of exercise, while this volume increased to a lesser degree in P- and controls ($p<0.001$). End-expiratory volumes of RC_A increased during exercise in a similar way in P+ and P- groups, while in healthy subjects they remained constant up to ~60% of the maximum workload and then increased on average by 316 mL at end-exercise. In healthy subjects, the V_{ab} at end-expiration fell significantly throughout the exercise, while at end-exercise the two COPD groups reached values identical on average to those measured during QB.

Symptoms and self-paced exercise

Data for the symptom intensity of dyspnoea and leg effort for both incremental and self-paced exercise and total distance walked for both P+ and P- patients are presented in table 2, while the symptoms at rest, the mid-point of exercise testing and end-exercise are shown in figure 8. The intensity of dyspnoea reported at end-exercise was similar in the two groups with both types of exercise. However, the symptom intensity of leg effort was significantly less in P+ patients during incremental exercise ($p<0.01$), with a similar trend in the self-paced walk test ($p<0.05$). The difference between dyspnoea and sense of leg effort severity was statistically significant in both types of test ($p<0.01$). Oxygen saturation and HR data did not show significant differences between P+ and P- groups for either corridor walking or cycling test.

DISCUSSION

Although the movement of the ribcage during the respiratory cycle normally tracks the change in lung volume, this is not always the case in patients with obstructive lung disease, as has been recognised by clinicians for many years [5, 6]. Magnetometer studies have identified different patterns of behaviour in the upper and lower ribcage [2, 7, 8] but the present data are the first to provide a quantitative three-dimensional assessment of the effect of lower ribcage paradox on chest wall volumes, ventilatory pattern and symptoms at rest and during exercise. It was observed that COPD patients

TABLE 2 Resting and end-exercise ventilatory pattern and metabolic and cardiac variables

	Control		COPD					
			All		P+		P-	
	Rest	Peak exercise	Rest	Peak exercise	Rest	Peak exercise	Rest	Peak exercise
Subjects n	10		20		8		12	
f_R breaths·min^{-1}	16±4	28±5	21±4	31±8	22±3	31±7	20±5	30±9
V_T L	0.67±0.12	2.45±0.58	0.86±0.26	1.42±0.36	0.80±0.16	1.42±0.29	0.89±0.30	1.41±0.41
V'_E L·min^{-1}	11.4±2.7	67.40±17.20	16.34±3.59	40.54±8.92	16.65±3.25	42.00±9.38	16.13±3.92	39.58±8.89
t_I s	1.50±0.26	1.04±0.19	1.07±0.29	0.87±0.38	1.03±0.27	0.79±0.29	1.11±0.32	0.94±0.45
Duty cycle %	39.6±6.0	46.2±2.5	35.6±5.4	39.8±5.8	34.7±5.6	39.4±5.3	36.1±5.6	40.1±6.5
V'_{O_2} L·min^{-1}	0.33±0.10	1.75±0.42	0.32±0.06	0.78±0.19	0.34±0.0	0.75±0.18	0.31±0.07	0.80±0.20
V'_{O_2} mL·kg^{-1}·min^{-1}	4.45±1.57	22.73±5.02	4.56±1.31	11.08±3.16	4.69±1.29	10.37±2.59	4.48±1.37	11.55±3.52
V'_{CO_2} L·min^{-1}	0.27±0.07	2.19±0.59	0.28±0.06	0.77±0.19	0.30±0.05	0.74±0.18	0.27±0.06	0.78±0.21
RER	0.83±0.11	1.25±0.11	0.87±0.07	0.98±0.10	0.89±0.05	0.99±0.10	0.86±0.08	0.97±0.11
P_{ET,CO_2} mmHg	35.5±4.3	39.5±4.7	29.9±5.0	33.3±5.9	30.7±7.1	35.6±7.5	27.6±3.3	31.6±4.1
Sa_{O_2} %	97±4	96±3	93±3	93±2	95±1	93±1	92±3	92±2
Heart rate beats·min^{-1}	89±19	120±12	93±14	122±17	94±10	121±4	93±20	124±18
Dyspnoea	0±0.0	4.4±3.8	0.7±0.2	4.0±1.1	0.9±0.9	3.9±0.8	0.7±0.7	4.1±1.2
Sense of leg effort	0±0.0	5±3.6	0.5±0.2	4.3±1.6	0.5±0.9	3.7±1.6	0.5±0.77	4.7±1.4**
Predominant symptom#	0±0.0	-0.6±0.6	0.2±0.1	-0.3±0.2	0.4±0.7	0.3±1.2	0.2±0.4	-0.7±0.7**
Maximum workload W	153±35		43±19		42±20		44±19	
6-min walking distance m			291±12		290±93		291±63	

Data are expressed as mean±SD. COPD: chronic obstructive pulmonary disease; P+: subjects showing lower ribcage inspiratory paradox at rest; P-: subjects without paradox; f_R: respiratory frequency; V_T: tidal volume; V'_E: minute ventilation; t_I: inspiratory time; V'_{O_2}: oxygen consumption; V'_{CO_2}: carbon dioxide production; RER: respiratory exchange ratio; P_{ET,CO_2}: end-tidal carbon dioxide tension; Sa_{O_2}: arterial oxygen saturation. #: dyspnoea minus leg effort. **: p<0.01 for comparison of P+ with P-. 1 mmHg=0.133 kPa.

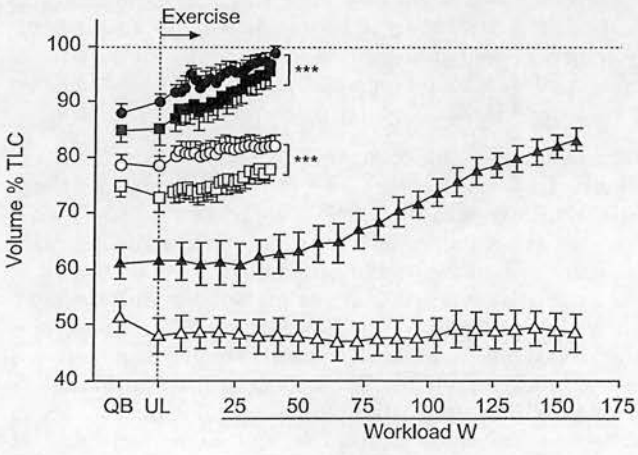

FIGURE 5. Mean±SE end-expiratory (EE) and end-inspiratory (EI) total chest wall volume variations during exercise, expressed as percentage of the chest wall volume at total lung capacity (TLC), in chronic obstructive pulmonary disease (COPD) patients and control subjects. ●: COPD subjects showing lower ribcage inspiratory paradox at rest (P+), EI; ■: COPD subjects without paradox (P-), EI; ○: P+, EE; □: P-, EE; ▲: control subjects, EI; △: control subjects, EE. QB: quiet breathing; UL: unloaded exercise. ***: p<0.001 for comparison of P+ with P- (overall data).

with paradox increased their EEV_{CW} as soon as exercise began, while those without lower ribcage paradox only hyperinflated their chest wall towards the end of incremental exercise. These changes were reflected in the symptoms reported during exercise, with dyspnoea being the major complaint when paradox was present, irrespective of whether the exercise was incremental or self-paced. This suggests that different patterns in the timing of EEV_{CW} change [12] relate to patient symptoms and can be reliably predicted by ribcage movement assessed under resting conditions.

In the present study, paradoxical ribcage movement was defined by quantifying the asynchrony between the two ribcage regions during inspiration. The current authors followed the model proposed by WARD *et al.* [20] and used by others reporting data with OEP [1, 4], in which the ribcage is considered as formed by two subcompartments, *i.e.* the part that is apposed to the lung, the RC_P, and the part apposed to the diaphragm, the RC_A. The boundary between the RC_P and the RC_A was defined by a surface identified by a set of markers placed at the level of the xiphisternum (fig. 1), which does not change with diaphragm movement. Thus, in COPD patients, the V_{RCA} may not precisely correspond to the true area of apposition but is best considered as representing the lower ribcage where the muscles inserted and acting in that area differ from those influencing upper ribcage volume.

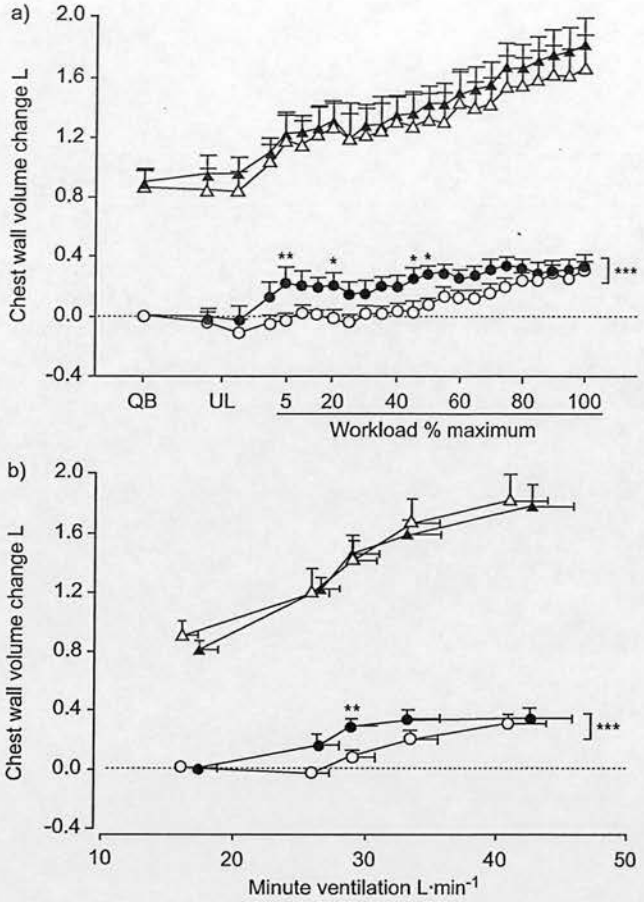

FIGURE 6. Mean±SE end-expiratory (EE) and end-inspiratory (EI) total chest wall volume variations during exercise, expressed as chest wall volume variations at functional residual capacity during quiet breathing (QB) in the chronic obstructive pulmonary disease (COPD) patients as a function of a) workload and b) minute ventilation. ▲: COPD subjects showing lower ribcage inspiratory paradox at rest (P+), EI; △: COPD subjects without paradox (P-), EI; ●: P+, EE; ○: P-, EE. UL: unloaded exercise. *: $p<0.05$ for comparison of P+ with P- (at same level of exercise); **: $p<0.01$ for comparison of P+ with P- (at same level of exercise); ***: $p<0.001$ for comparison of P+ with P- (overall data).

While previous studies have used changes in the lateral and antero-posterior dimensions of the ribcage to do this [7, 8], the present approach was based on the analysis of volume variation, obtained by integrating the three-dimensional motion of multiple surface markers. Thus, the current data are not strictly comparable with those obtained by two-dimensional analysis of lower ribcage movement alone, and they provide a description of normal or paradoxical inspiratory motion that includes and integrates changes of dimensions in multiple directions. A conservative definition of paradox based on the relative movement of the upper and lower ribcage regions was used, which was only considered to be significant when there were changes beyond the normal range in both the percentage of inspiratory time where paradox was seen and in the phase angle shift. The latter index provided a measure of the degree of chest wall distortion while the former indicated how much of the inspiratory period was affected. It was possible to classify individuals in a binary fashion, although the variables themselves are likely to represent a continuous spectrum of severity as can be seen in figure 3 and supplementary table E1. Each of these measurements proved relatively reproducible in both healthy subjects and those with COPD when different breaths were ensemble-averaged to generate the data. Moreover, differences in individual operators positioning the markers on different days did not influence the results, nor did the classification of resting paradoxical ribcage movement change if different breaths were used to define it.

When a different index like the hysteresivity of the V_{RCp}–V_{RCa} loop was considered instead of the phase shift angle, the classification did not change substantially. Only one patient who previously showed an increased percentage inspiratory paradox without an apparently abnormal phase angle shift would have been reclassified as belonging to the P+ group. Interestingly, this patient showed relatively early onset of chest wall hyperinflation during exercise.

The present data were primarily observational rather than mechanistic. Like the investigators who identified Hoover's sign clinically [9, 21], the current authors found no relationship between the presence of lower ribcage paradox and resting lung function. The only significant differences found between P+ and P- groups were for weight and body mass index, suggesting that paradox may be commoner as weight increases. This needs to be confirmed in a larger population of patients. However, a selective activation of different respiratory muscle groups might explain the relationship between the presence of ribcage paradox at rest and the increased end-expiratory V_{RCp} at the onset of exercise in the P+ subjects. These patients may exhibit an increase in ribcage and related accessory muscle tonic activation. More detailed studies to understand the basis of resting paradox defined as in the present study are now underway. Future experiments are needed in order to correlate paradoxical movement of the lower ribcage to diaphragm shape and length of the area of apposition, as recently proposed by preliminary studies based on ultrasound [2, 22, 23] and magnetic resonance [24] imaging.

Exercise modified the different components of paradox in different ways. In controls and P- COPD subjects, the phase angle was unchanged by exercise, while in P+ patients it only decreased at maximum workload, but even then did not reach the values seen in the healthy subjects and P- COPD patients. This result may reflect the increasing volume, and therefore decreasing compliance, of the RC_p as hyperinflation develops, with a concomitant increase in the mechanical linkage between the two ribcage portions. In contrast, in the control and P- subjects, the percentage of inspiratory paradox time tended to increase at the onset of exercise and to remain constant thereafter, approaching levels similar to those seen in the P+ group. This result may be attributed to the insertional action of the expiratory abdominal muscles on the lower ribcage [1, 4], even though end-expiratory V_{ab} decreased substantially only at the onset and during exercise in the healthy subjects (fig. 7).

All the P+ patients showed an early increase of EEV_{cw}. This was mainly due to the increase of the V_{RCp}, presumably to cope with the expiratory action of the lower ribcage, which was not seen in

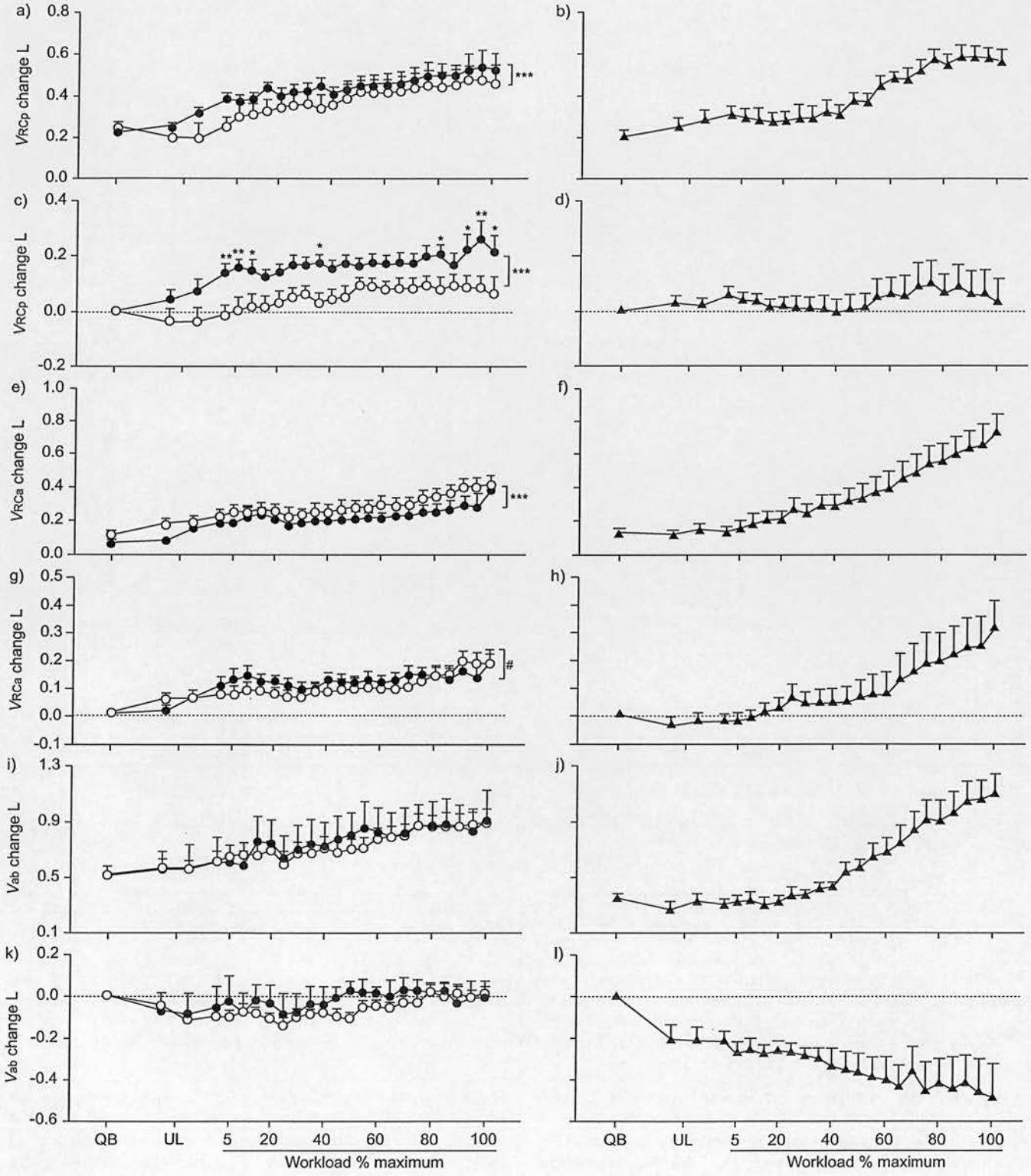

FIGURE 7. Mean ± SE end-inspiratory (a, b, e, f, i and j) and end-expiratory (c, d, g, h, k and l) volume variations of the upper ribcage (V_{RCp}; a–d), lower ribcage (V_{RCa}; e–h) and abdomen (V_{ab}; i–l) during exercise in the chronic obstructive pulmonary disease (COPD; a, c, e, g, i and k) and control groups (b, d, f, h, j and l). All volumes refer to the corresponding values at functional residual capacity during quiet breathing (QB). ●: COPD subjects showing lower ribcage inspiratory paradox at rest (P+); ○: COPD subjects without paradox (P-); ▲: control subjects. UL: unloaded exercise. *: $p<0.05$ for comparison of P+ with P- (at same level of exercise); **: $p<0.01$ for comparison of P+ with P- (at same level of exercise); ***: $p<0.001$ for comparison of P+ with P- (overall data); #: $p<0.05$ for comparison of P+ with P- (overall data).

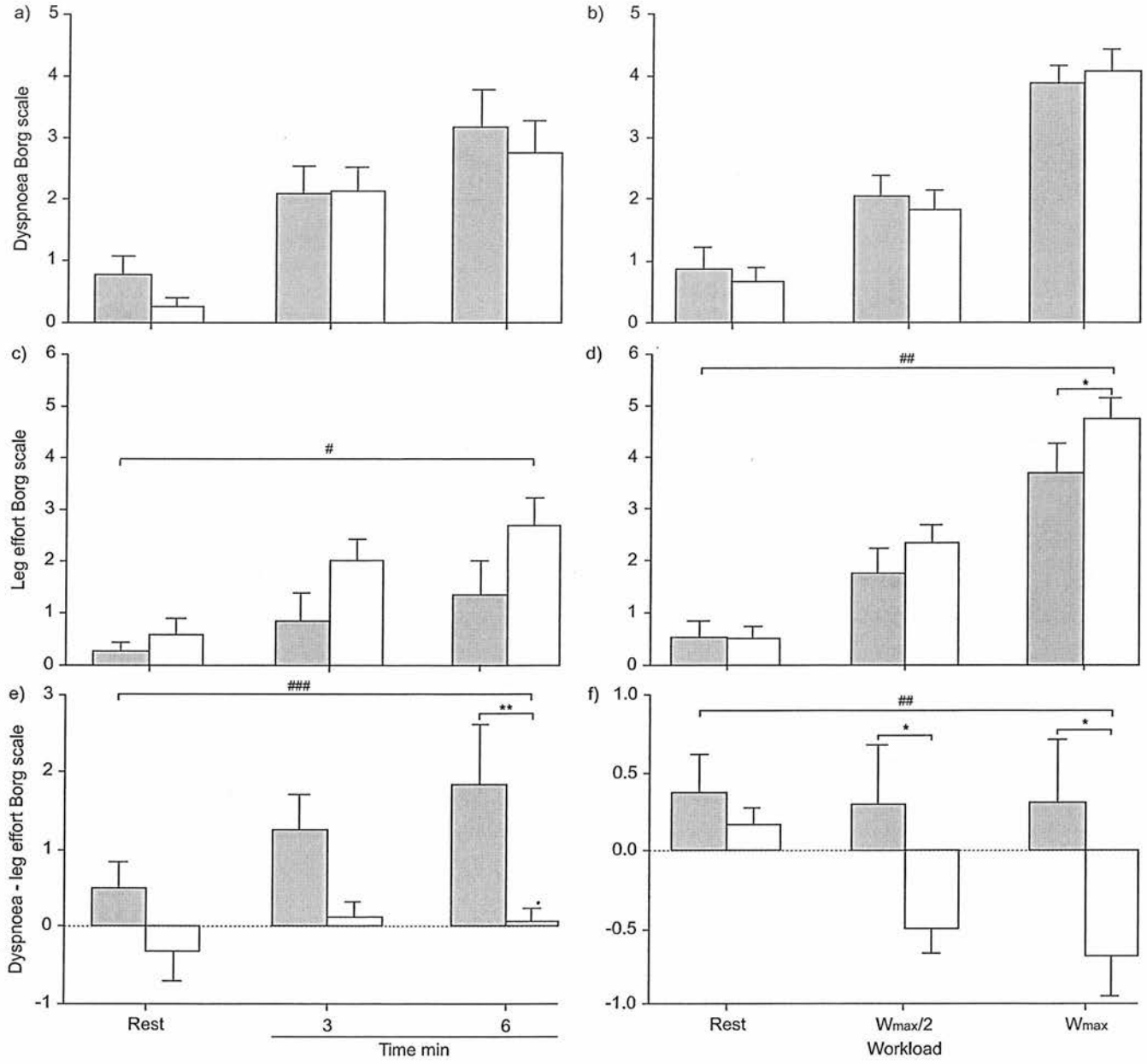

FIGURE 8. a and b) Dyspnoea, c and d) leg effort and e and f) difference between the two symptoms (dyspnoea minus leg effort) during the 6-min walking test (a, c and e) and exercise (b, d and f). Data are presented as mean±SE. ▨: chronic obstructive pulmonary disease (COPD) subjects showing lower ribcage inspiratory paradox at rest (P+); □: COPD subjects without paradox (P-). Wmax: maximum workload exercise. *: $p<0.05$ for comparison of P+ with P- (at same level of exercise); **: $p<0.01$ for comparison of P+ with P- (at same level of exercise); #: $p<0.05$ for comparison of P+ with P- (overall data); ##: $p<0.01$ for comparison of P+ with P- (overall data); ###: $p<0.001$ for comparison of P+ with P- (overall data).

the P- patients. The early onset of chest wall hyperinflation in P+ patients was unexpected and was not related to the duration of exercise or the severity of airflow obstruction or baseline pulmonary hyperinflation. Retrospective classification of the presence of tidal expiratory flow-limitation showed that all the eight P+ patients were flow-limited compared with nine out of the 12 P- patients. None of the P- patients exhibited chest wall hyperinflation at the onset of exercise. These results suggest that paradoxical motion rather than the presence of tidal expiratory flow-limitation determines early chest wall hyperinflation.

Breathlessness and sense of leg effort increased during exercise in patients with and without ribcage paradox, although the relative importance of each symptom differed. At the end of cycle exercise, end-inspiratory V_{CW}, which is not influenced by gas compression and blood shift effects, approached the critical inspiratory reserve volume associated with neuromechanical dissociation [25] in both groups. However, the P+ patients were less likely to report severe sense of leg effort than the P- patients, with breathlessness being their principal complaint at the end of exercise. This is in keeping with previous reports of

symptom limitation in severe COPD [26], and the predominance of effort in P- subjects was replicated during the self-paced corridor testing. These differences were not related to degree of oxygen desaturation, peak workload or exercise duration. The early onset of dynamic hyperinflation of the chest wall is the most likely explanation for the predominance of dyspnoea in P+ patients. In P- patients other factors, such as the onset of peripheral muscle fatigue that limits exercise in some COPD patients, may have been more important [27].

The present study was designed to identify reliable objective criteria for the presence of paradoxical lower ribcage movement and test whether these could be used to predict physiological differences during exercise in stable hyperinflated COPD patients. Although the criteria resemble the subjective ones described by HOOVER [6], the current patients were not selected on the basis of a clinical diagnosis of Hoover's sign and this was not recorded, to avoid the risk of biasing the results. Other studies have examined resting lower ribcage movement using the OEP method in patients clinically defined as having Hoover's sign, and have reported that Hoover's sign did not correlate with the level of hyperinflation and, therefore, ribcage distortion and hyperinflation appear to be independent factors limiting ventilatory function in stable COPD patients [21].

In conclusion, the present study has shown that abnormal lower ribcage movement is not just a clinical curiosity but that it identifies important physiological differences in the chest wall volumes during exercise and these translate into different patterns of reported symptoms. The early onset of hyperinflation in those with paradox helps to explain why differences seen in incremental exercise are still present during lower-intensity self-paced exercise, which relates to the daily activity undertaken by chronic obstructive pulmonary disease patients.

ACKNOWLEDGEMENTS

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Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations

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Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. P.W. Jones, L.R. Willits, P.S. Burge, P.M.A. Calverley, on behalf of the Inhaled Steroids in Obstructive Lung Disease in Europe study investigators. ©ERS Journals Ltd 2003.

ABSTRACT: Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with worse health and increased healthcare utilisation. The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study in COPD showed a 26% reduction in the yearly rate of exacerbations in patients treated with fluticasone propionate (FP) compared to placebo, but did not indicate which patients showed greatest benefit.

In this study the patients were stratified into mild and moderate-to-severe COPD using the American Thoracic Society criterion of forced expiratory volume in one second (FEV_1) 50% predicted, and the total number of exacerbations and those requiring treatment with oral corticosteroids were examined.

There were 391 (195 FP) patients with mild COPD and 359 (180 FP) patients with moderate-to-severe disease. The exacerbation rate was highly skewed in mild disease, but more normally distributed in moderate-to-severe disease. FP reduced the overall exacerbation rate in moderate-to-severe disease (FP median rate 1.47 yr^{-1}, placebo 1.75 yr^{-1}), but not in mild disease (FP 0.67 yr^{-1}, placebo 0.92 yr^{-1}). FP use was associated with fewer patients with ≥ 1 exacerbation·yr^{-1} being treated with oral corticosteroids (mild: FP 8%, placebo 16%; moderate-to-severe: FP 17%, placebo 30%).

Effects of fluticasone propionate on exacerbations were seen predominantly in patients with a postbronchodilator forced expiratory volume in one second <50% predicted. These data support recommendations in the Global Initiative for Chronic Obstructive Disease treatment guidelines that inhaled corticosteroids should be considered in patients with moderate-to-severe chronic obstructive pulmonary disease who experience recurrent exacerbations.

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Exacerbations in chronic obstructive pulmonary disease (COPD) are common and associated with significant impairment of health status [1]. Hospitalisation is relatively frequent [2]. The total cost of treating exacerbations of COPD in the USA has been reported to be US$ 1.2 billion, with inpatient and outpatient care accounting for US$ 32 million and US$ 452 million, respectively [3].

International guidelines recommend bronchodilators as first-line treatment for COPD symptom control [4–6], since there no evidence to suggest that such agents slow the progression of the disease [7]. Studies with inhaled corticosteroids have failed to show a reduction in rate of decline in forced expiratory volume in one second (FEV_1) in COPD [8–13]. By contrast, there is evidence to suggest that these agents may reduce the rate and severity of COPD exacerbations defined clinically and by the use of additional treatment [8, 11].

The recent Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, investigated the effect of inhaled fluticasone propionate (FP) 500 μg twice daily for 3 yrs on the rate of decline of FEV_1 and other clinical outcomes [12]. FP treated patients had a significantly greater postbronchodilator FEV_1 than placebo throughout the trial, although the rate of decline in FEV_1 was not altered. FP did reduce the median yearly exacerbation rate by 25% and significantly reduced the rate of deterioration in health status. The initial report presented the intention-to-treat analysis of these data, but did not consider whether all patients showed similar treatment benefits. In this study a *post hoc* analysis to determine whether existing criteria for disease severity identifies patients with a different probability of exacerbating and whether the effect of inhaled corticosteroids on acute exacerbations is influenced by disease severity are reported.

Methods

Full details of the study methodology, patient selection, efficacy assessments and statistical analyses have been published previously [12].

Patients

In brief, the study enrolled current or former smokers aged 40–75 yrs with nonasthmatic COPD. Patients were excluded due to the following: they had ever received a diagnosis of asthma, FEV1 improved by >10% predicted normal following 400 μg inhaled salbutamol, the postbronchodilator FEV1 was <0.8 L at study entry or they had clinically significant concurrent medical conditions or a condition likely to reduce life expectancy to <5 yrs.

Study design

The study used a randomised, double-blind, placebo-controlled, parallel-group design. It was conducted in 18 hospitals in the UK. All patients provided written informed consent and the protocol was approved by each local research ethics committee.

Patients using inhaled corticosteroids discontinued them and all entered an 8 week-run-in period to ensure clinical stability and establish the baseline pre- and postbronchodilator spirometry. After this, patients were asked to participate in a 2-week trial of oral corticosteroids (0.6 $mg \cdot kg^{-1} \cdot day^{-1}$). The majority did so (85%), but those who did not proceeded directly into the randomised study. Classification of patient severity was made using FEV1 measurements obtained before any corticosteroid was given.

Patients were withdrawn from the study if continuance was considered detrimental to the patient or if they required more than two short courses of oral corticosteroids in any 3-month period or maintenance oral or inhaled corticosteroid treatment.

Treatment

At the end of the run-in period, patients were randomised to receive FP 500 μg twice daily *via* metered-dose inhaler and Volumatic™ (GlaxoSmithKline, Greenford, UK) spacer device or an identical placebo. Randomisation was carried out centrally using a computer program and treatment allocation codes were not available to the trialists. Other medication was continued throughout the study and was equally distributed in terms of dose of drug and frequency of use between the treatment groups.

Efficacy

The principal outcome in this analysis was the number of exacerbations per year. An exacerbation was defined as "chest problems requiring treatment with antibiotics and/or oral corticosteroids". It had been anticipated that, in this 3-yr study the great majority of exacerbations would be treated by primary care physicians and it was judged to be impossible to set criteria for the diagnosis of an exacerbation to be used by several hundred primary care physicians. Exacerbations were recorded by patient self-report at 3-monthly intervals. Treatment of each exacerbation was recorded, specifically whether the attending doctor prescribed antibiotics, oral corticosteroids or both. The physician treating these episodes was unaware of the trial treatment the patient was receiving.

Statistical analysis

The results were analysed first in the intention-to-treat (ITT) population (defined as all patients who were randomised to treatment and who received at least one dose of study medication), then in two subgroups, categorised on the basis of the American Thoracic Society criteria for severity [4] as follows: mild (postbronchodilator FEV1 $\geq$50% pred) and moderate-to-severe (postbronchodilator FEV1 <50% pred).

The exacerbation rate for each patient was calculated as the number of exacerbations experienced per year. If a patient withdrew during the study, the exacerbation rate was calculated by dividing the number of exacerbations experienced during the treatment period by the time spent on treatment. Exacerbations were analysed as follows: 1) all exacerbations regardless of how treated; or 2) exacerbations treated with oral steroids, either alone or in combination with antibiotics. The difference between treatments was tested using the van Elteren extension to the nonparametric Wilcoxon Mann-Whitney rank-sum test [14]. Study centre was used as a stratifying variable in the analysis. Confidence intervals (CI) for treatment differences were calculated by pooling all the treatment differences using the Hodges-Lehman method [15]. Stratification by study centre was not considered in this calculation.

The effect of treatment on the proportion of patients experiencing one or more exacerbations in each year of the study (cumulative) was tested using Fisher's exact test [16]. The relationship between treatment and time to onset of the first exacerbation was analysed using survival analysis techniques and the log-rank test (5% significance level). The time to the first exacerbation was also modelled using Cox's proportional hazards model [17]. The covariates considered for inclusion in the model were age, smoking status, sex, study centre and baseline FEV1. Distribution statistics for parametric data are reported as SD.

Results

Patient demography

A total of 751 patients were randomised to treatment, 376 to FP and 375 to placebo.

Both treatment groups were well matched at baseline [12]. The baseline and demographic data were similar for patients with mild and moderate-to-severe COPD (table 1). There were small differences between the two subgroups, with significantly more males than females with mild rather than moderate-to-severe disease (85 *versus* 65%, $p<0.0001$). The number of pack-yrs smoked was higher in the moderate-to-severe

Table 1.–Patient characteristics at baseline

Characteristics	Moderate-to-severe FEV1 <50% pred		Mild FEV1 ⩾50% pred	
	Placebo	FP	Placebo	FP
Subjects n	195	196	179	180
Age yrs	64±7	64±6	63±8	63±8
Male %	81	86	66	63
Smoking history				
Pack-yrs	48±36	47±30	39±31	42±30
Current smokers %	38	32	41	41
Exsmokers %	48	51	44	43
Intermittent %	14	17	16	16
Atopy[#] %	14	13	11	14
FEV1[¶] L	1.0±0.2	1.0±0.3	1.6±0.5	1.6±0.5
FEV1 % pred	39±8	39±8	62±10	62±10
% FEV1 reversibility[+]	4.1±3.4	4.2±3.4	4.8±3.4	4.6±3.6

Data are presented as mean±SD; FEV1: forced expiratory volume in one second; FP: fluticasone propionate; % pred: % predicted; [#]: atopy defined as positive skin-prick test to one or more common allergens; [¶]: prebronchodilator FEV1; [+]: change in FEV1 after bronchodilator expressed as % pred. There were no significant differences (p>0.05) between the treatment groups, within each severity category, for any variable. Except for proportionally more females in the mild compared to the moderate-to-severe group (p<0.001) and more pack-yrs smoked in the moderate-severe group.

group than in the mild group (47 *versus* 41, p<0.01), but the proportion of continued, mixed and exsmokers was the same in the two groups (p>0.05).

Onset of first exacerbation

Kaplan-Meier analysis of the ITT population showed no difference in the time to first exacerbation, p=0.34. Using Cox's proportional hazards model for the time of onset of the first exacerbation, the median time in the placebo group was 136 days *versus* 164 days in the FP group (95% CI 0.79–1.09, p=0.35).

Number of exacerbations and withdrawals

Analysis of the total number of exacerbations showed no significant difference between the two treatment groups. During the first year of treatment, 227 patients in the FP group (61%) and 237 in the placebo group (64%) had at least one exacerbation. Similarly, 290 (78%) and 286 (77%) patients, respectively, experienced at least one exacerbation during the 3-yr study period. During the study, 355 patients were withdrawn, 160 in the FP group and 195 in the placebo group. The most common reason for withdrawal was frequent exacerbations of COPD; 42 FP patients, 54 placebo patients. Placebo-treated patients were also more likely to be withdrawn earlier than FP patients [12]. As a result of the earlier and greater drop-out rate, placebo patients spent less time in the study (758 patient-yrs) than those treated with FP (840 patient-yrs).

Frequency of exacerbations

The annualised rate of exacerbations ranged from 0 to ⩾8 yr^{-1}. The distribution was highly skewed in the mild patients, but more normally distributed in those with moderate-to-severe disease. Over the 3-yr period, 29% of the mild patients had no exacerbations at all, but this was seen in only 16% of those with moderate-to-severe disease (fig. 1). The median exacerbation rate in the combined treatment groups was significantly lower in the mild patients (0.93 yr^{-1}) compared to those with moderate-to-severe disease (1.64 yr^{-1}), p<0.0001.

In the ITT population, there were fewer exacerbations in the FP-treated group (0.99 exacerbations·yr^{-1}) compared with placebo (1.32 exacerbations·yr^{-1}), p=0.026. The significant effect of FP was confined to the moderate-to-severe group: FP median 1.47 exacerbations·yr^{-1}; placebo 1.75 exacerbations·yr^{-1}, p<0.022 (fig. 2). There was no statistically significant effect in the mild group (FP median 0.67 exacerbations·yr^{-1}; placebo 0.92 exacerbations·yr^{-1}, p=0.45). The frequency of exacerbations in the two patient groups remained unchanged throughout the 3 yrs of the study. In both treatment groups, neither the median rate nor the 'tail'

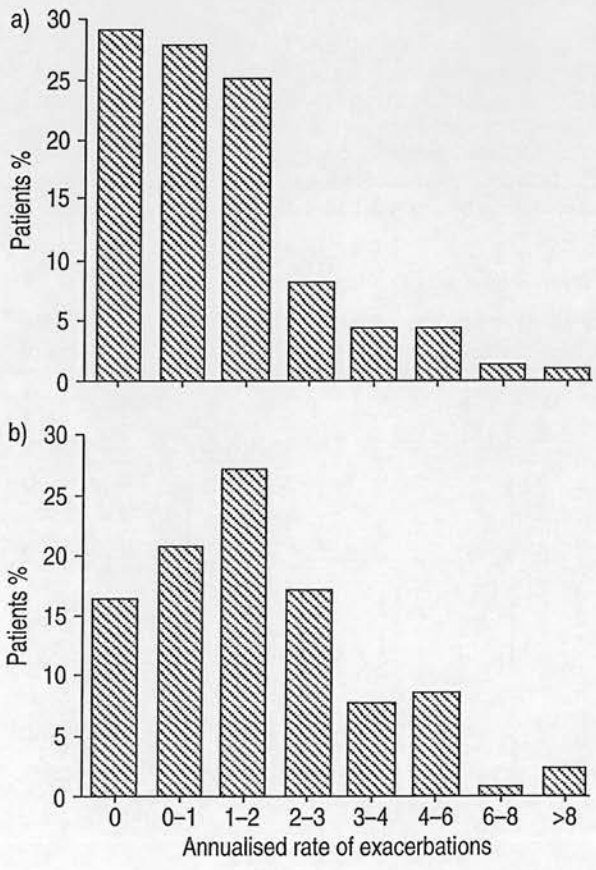

Fig. 1.–Frequency distribution for exacerbation rate per year in patients with a) mild and b) moderate-to-severe chronic obstructive pulmonary disease. In mild patients the distribution was highly skewed whereas in moderate-to-severe disease the distribution was more normally distributed.

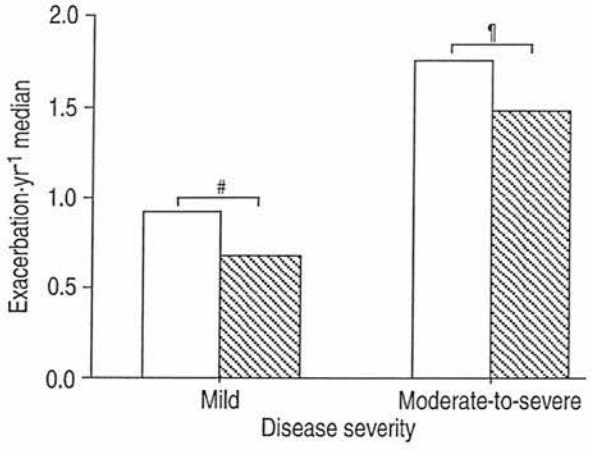

Fig. 2.–Bar chart of the median rate of exacerbations per year in placebo (□) and fluticasone propionate (▨) treated patients, split by disease severity (American Thoracic Society criteria). The Mann-Whitney rank-sum test was used to calculate p-values. #: p=0.45; ¶: p=0.022.

of patients with high numbers of exacerbations per year appeared to lessen.

Exacerbations treated with steroids

In patients with moderate-to-severe disease, 52% had a corticosteroid-treated exacerbation compared to 30% of the mild group (Fisher's exact test $p<0.0001$). The rate of these exacerbations was significantly lower in FP-treated patients compared to placebo, $p<0.001$. FP halved the number of patients having one or more exacerbations per year in both patient groups (fig. 3).

Reversibility and exacerbations

To test for the presence of subgroups of patients with a greater effect of inhaled corticosteroid, further

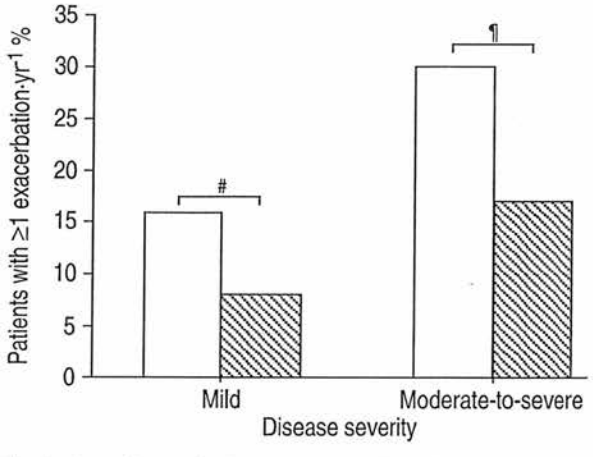

Fig. 3.–Bar chart of the percentage of patients having ≥1 corticosteroid-treated exacerbation·yr^{-1} in placebo (□) and fluticasone propionate (▨) treated patients, split by disease severity (American Thoracic Society criteria). The Mann-Whitney rank-sum test was used to calculate p-values. #: p=0.02; ¶: p=0.01.

post hoc analyses were carried out, dividing patients into those with greater or less reversibility to bronchodilator (median split cutting at 170 mL) and those with greater or less response to prednisolone (median split cutting at 50 mL). In none of these subgroups was the effect of fluticasone statistically significant ($p>0.05$ in each case).

Discussion

Reducing the number of exacerbations of COPD is an important goal of treatment and has been stressed in several treatment guidelines [4–6]. In patients treated with FP, the rate of exacerbations was reduced compared to the placebo-treated patients. This effect was confined to patients with more severe airflow limitation, since the difference between treatment groups was not statistically significant in the milder patients. This could represent a genuine difference in efficacy dependent on disease severity or be a reflection of the smaller number of episodes identified in mild disease and hence the risk of a Type 2 statistical error, since the proportional reduction was the same. Support for the latter view comes from the report of a beneficial effect of inhaled triamcinolone on emergency physician contacts in the recent large Lung Health Study II in patients with mild COPD [13].

Not all exacerbations were treated with oral steroids. Half of the patients with moderate-to-severe disease received at least one course compared with less than one third in those with mild disease. The reasons for this are not clear from the current study, but it is possible that doctors were more likely to prescribed oral steroids in patients with worse airflow limitation or those who appear to have more severe attacks. This conclusion is supported by data from a large Spanish community study in which prescription of oral corticosteroids was strongly related to the intensity of dyspnoea [18]. In both severity subgroups, FP halved the number of patients who needed one or more courses of oral corticosteroids in a year. In patients with moderate-to-severe disease it reduced the proportion of patients requiring oral corticosteroids to the level of those with mild disease treated with placebo.

The median exacerbation rate in the placebo-treated patients in this study was 1.3·patient^{-1}·yr^{-1}. This is similar to that in a large series of patients assessed for antibiotic treatment [19] and to the rate of 1.5·patient^{-1}·yr^{-1} reported in COPD patients with a similar disease severity in the UK [1]. The similarity in exacerbation rate between the latter study and the present study occurred despite two major differences between the studies. First, there were differences in definition of an exacerbation: increased cough and dyspnoea for ≥2 days used by SEEMUNGAL *et al.* [1] and chest problems requiring treatment with antibiotics and/or oral corticosteroids used in this study. Secondly, in the current study details of exacerbations were recorded retrospectively at 3-month intervals, whereas SEEMUNGAL *et al.* [1] collected their exacerbation data prospectively using diary cards. Furthermore, in the

current study there was also the potential to lose the effect of patients with the highest frequency of exacerbations because of the study criterion, which required withdrawal if three courses of oral steroids were needed in any 3-month period. However, this effect will have been small, since the tail of the frequency distribution curve of exacerbations contained only 9% of patients with an exacerbation rate >4 yr^{-1}, even in patients with moderate-to-severe COPD (fig. 1).

The frequency of exacerbations was significantly higher in patients with moderate-to-severe as compared to mild airflow limitation. Patients with mild disease had, on average, <1 exacerbation·yr^{-1} whereas those with moderate-to-severe disease had >1.5 exacerbations·yr^{-1}. Although the frequency distribution of the exacerbations was skewed towards relatively infrequent acute episodes, a quarter of moderate-to-severe patients still had >3 exacerbations·yr^{-1}. At the other end of the spectrum, during the entire 3-yr period, there were no acute episodes recorded in 16% of the moderate-to-severe patients who received placebo and 29% in those with mild disease. These data support the thresholds, based on FEV1, that are used in a number of treatment guidelines to identify patients at risk of greater morbidity [4].

The findings of the present study support earlier data in which, compared with placebo, FP significantly reduced the incidence of severe exacerbations, defined by the need for hospitalisation [8], however, FP had no effect on the time to first exacerbation. This may have been due in part to imprecision in the capture of the time of the first exacerbation, which in large measure depended on the patient's recall of the event when questioned at their 3-monthly visit. The total number of patients who experienced an exacerbation was also not influenced by FP. One interpretation of these observations is that the drug was having an effect in patients who were prone to recurrent exacerbations. This view is consistent with the finding that the treatment effect was most evident in patients with moderate-to-severe airflow limitation, who were also the group that had more frequent exacerbations and were more likely to be treated with courses of oral steroids in addition to antibiotics.

The parallel-group design of these placebo-controlled studies permits the conclusion that FP use was associated with a lower exacerbation frequency. The hypothesis that FP reduces exacerbation frequency can only be tested directly in a study in which patients act as their own controls and exacerbation frequency is measured before and after the introduction of the treatment. Such a study would require a crossover design and need either a very large number of patients or long duration in each arm to ensure adequate power. It is probably not practically possible to launch such a trial.

In conclusion, this analysis has shown that exacerbations are more frequent in patients with moderate-to-severe chronic obstructive pulmonary disease, a quarter of whom may require treatment with antibiotics and/or oral steroids three times in the course of a year. Fluticasone propionate significantly reduced both the rate of exacerbations in chronic obstructive pulmonary disease and the number of exacerbations treated with courses of oral corticosteroids. This effect was most apparent in patients with moderate-to-severe disease. Therefore, patients with moderate-to-severe chronic obstructive pulmonary disease and a history of recurrent exacerbations appear to be those most likely to benefit from this therapy, as proposed in the recent Global Initiative for Chronic Obstructive Lung Disease management guidelines [20].

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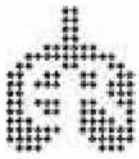

Relationship between respiratory symptoms and medical treatment in exacerbations of COPD

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ABSTRACT: Exacerbations of chronic obstructive pulmonary disease (COPD) can be defined symptomatically or by healthcare contacts, yet the relationship between these events is unknown. Data were collected during a 1-yr study of the budesonide/formoterol combination in COPD patients, where exacerbations, defined by increases in treatment, were compared with daily records of respiratory symptoms, rescue medication use and peak expiratory flow (PEF).

The relationship between changes in these variables and the medical event was examined using different modelling approaches. Data from the first exacerbation treated with oral corticosteroids and/or antibiotics and/or hospitalisation (event based) were available in 468 patients.

Patients exacerbating were significantly more breathless and more likely to report cough than healthy patients, but did not differ in baseline spirometry. Exacerbations defined by changes in individual symptoms were only weakly related to event-based exacerbations; however, defined with 63% of such events being predicted from symptom changes. Changes in rescue medication use or PEF were poor predictors of event-based exacerbations. The mean peak change in symptoms was closely related to the onset of therapy.

In conclusion, event-based exacerbations are a valid way of identifying acute symptom change in a chronic obstructive pulmonary disease population. However, daily symptom monitoring is too variable using the current diary cards to make individual management decisions.

KEYWORDS: Chronic obstructive pulmonary disease, concurrence, events, exacerbations, symptoms

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, and is the only leading cause of death that is increasing in prevalence [1]. Acute exacerbations of COPD contribute significantly to the individual's disease burden, and an increased frequency of these episodes may hasten disease progression and possibly accelerate rate of decline in lung function [2–4]. Acute exacerbations are also associated with a poor prognosis, with hospital mortality rate ranging from 3–10% in severe patients [5, 6]. If intensive care unit admission is required, the rate is substantially higher, with >30% mortality in patients >65 yrs of age [7].

To understand the causes and evaluate treatment that could change the severity or frequency of exacerbations, a robust and reproducible definition of what constitutes an exacerbation is required. Several approaches to defining an exacerbation have been proposed and each has its disadvantages [8]. The most commonly used, and the one recognised most easily by patients themselves, involves a sustained increase beyond the normal variability in respiratory symptoms (dyspnoea, cough, sputum volume and sputum purulence) [9]. Other symptom-based definitions have been developed, but none have been validated in terms of their reliability and responsiveness [2, 10–14]. An alternative approach to definition identifies episodes where symptoms increase and there is a medical "event", *e.g.* a change of therapy (antibiotics or oral corticosteroids) or management (admission to hospital) [15–19]. This practical definition avoids the subjectivity of a change in symptoms and usually requires the involvement of a medical professional in the diagnostic process.

Although most clinicians assume that these approaches are broadly comparable, there has

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not been any direct comparison of events defined using these different approaches. The hypothesis presented here is that there would be a consistent increase in one or more key symptoms in the period around the time of any medical consultation defined as being an exacerbation. This would allow identification of discrete episodes that could form the basis of an automated exacerbation-detection algorithm. These concepts were tested by retrospectively analysing data collected as part of a large clinical trial, where event-based exacerbations were prospectively defined, and in which patients had recorded daily symptom and peak expiratory flow (PEF) data using a diary card approach validated in bronchial asthma [20]. The primary analysis of this clinical trial data has already been published [18].

METHODS

Study design and patients

The present study utilised data from a 12-month, randomised, placebo-controlled, parallel-group study of 796 patients with available data (patients experiencing at least one exacerbation) in 11 countries (mean age 64 yrs, mean forced expiratory volume in one second (FEV_1) 0.99L, 36% predicted). Subjects were randomly assigned to take two inhalations *b.i.d.* of the following: 9 μg formoterol; 400 μg budesonide; budesonide/formoterol combination in a dose of 320/9 μg respectively per inhalation; or placebo [18]. The study included one enrollment visit, one visit after a 2-week run-in period (visit two) and six subsequent visits during the treatment period.

Diary cards were distributed at visits one to seven and collected at visits two to eight. The diaries were carefully reviewed by the investigator together with the patient. Comments judged by the investigator to indicate an adverse event were noted in the appropriate section of the clinical record form.

The diary cards included the following daily recordings: 1) PEF morning and evening; 2) whether rescue medication was taken during the 6 h prior to PEF measurement; 3) daytime COPD symptom scores; 4) night-time awakenings due to COPD symptoms; 5) intake of study medication morning and evening; 6) intake of rescue medication and cough medicines (anti-tussives) morning and evening; and 7) intake of oral steroids, antibiotics, healthcare contacts and sick-leave related to COPD symptoms.

A mini-Wright peak flow meter (Clement Clark, Harlow, UK) and a diary card were dispensed at visit one. The patients were carefully instructed in the use of the peak flow meter. All measurements were to be made while standing. Rescue medication (bricanyl turbuhaler 0.5 $mg \cdot dose^{-1}$) was not to be taken for 6 h prior to PEF measurement. The patients were instructed to perform three manoeuvres twice daily (morning and evening), the highest value on each occasion being recorded in the diary. The morning measurement was made immediately upon rising before taking the study medication. Similarly, the evening measurement was made before going to bed and before the evening dose of study medication.

Definitions

Event-based exacerbations

Event-based exacerbations were defined as use of oral corticosteroids and/or antibiotics and/or hospitalisation for a worsening in the patient's respiratory symptoms at the discretion of their usual physician. These events were captured as severe exacerbations in the original study [18].

Symptom-based exacerbations

Symptom-based exacerbations were defined retrospectively in a variety of ways (see below) using data recorded daily in diary cards. Four symptoms (shortness of breath, cough, chest tightness and night-time awakenings) were each assessed on a scale of 0–4. The specific questions asked are listed in table 1. In addition, patients recorded daily use of short-acting β_2-agonist (rescue medication) and morning and evening PEF values. Diary cards were collected at each visit. Only diary card data related to the first event-based exacerbation during the 12-month follow-up are presented in the present study.

The day an event-based exacerbation was deemed to have occurred (*i.e.* day 0) was defined as the day on which hospital admission occurred or drug therapy was initiated, as identified on the diary card and/or a specific supplementary medicine record kept by the patient during the study and reviewed at the regular review visits. The number of symptom-based exacerbations occurring within 7 days of an event-based exacerbation was determined. Where overlap was seen, this was classified as "concurrence" and considered to be the same event. The maximum level of concurrence was, therefore, 100%.

Descriptive analysis

The event-based exacerbation defined in the clinical study was used as the "gold standard". The relationship between the change in symptoms, increased rescue medication use and per cent predicted morning and evening PEF were compared with the first event-based exacerbation that occurred. The definitions used for change in symptoms are described below. Table 1 shows the percentage of days during the run-in phase where the indicated score was recorded. For each, the average score for each patient during run-in was calculated and used as a variable.

This was an exploratory analysis in which statistical assessment of differences between groups was not appropriate, since there was no *a priori* hypothesis to test between the different classification systems.

Proposed classification systems

Simple symptom, rescue medication and PEF algorithm

Table 2 lists the analyses performed using a simple algorithm based on symptoms, rescue medication use and change in morning PEF. Further exploration by varying the time window for the exacerbation (3, 5 and 7 consecutive days, respectively) and time lag (28, 14 and 7 days before an event-based exacerbation, respectively) was also investigated.

Combined symptom scores

The various combined symptom scores explored in these analyses are also described in table 2. An arbitrary scale was developed for use in clarifying external rules that would allow definition of an exacerbation objectively or by automated means.

Subdivision of patients with event-based exacerbations

In order to examine the relationship between event- and symptom-based exacerbations, a number of exploratory

TABLE 1 Baseline age and forced vital capacity in one second (FEV_1) % predicted normal, and symptoms during run-in

	Symptoms	Patients with exacerbation#	Patients with no exacerbation#	p-values
Age yrs		64.1	64.1	
FEV_1 % pred		36.3	39.3	
Shortness of breath scores				
0	None: unaware of any difficulty	6.8	13.9	<0.001
1	Mild: noticeable during more strenuous activity, e.g. morning exercises, walking more than one block or up more than one flight without stopping	25.5	29.3	
2	Moderate: noticeable during light activity, such as making beds or taking out the garbage, walking one block or up one flight of stairs, running or jogging	41.7	37.6	
3	Marked: noticeable when washing or dressing in the morning, after slowly walking less than one block or up to one flight of stairs	21.0	16.7	
4	Severe: almost constant, present even when resting	5.0	2.5	
Cough scores				
0	No cough: unaware of coughing	22.7	26.4	<0.001
1	Rare: cough now and then	34.7	34.8	
2	Occasional: less than hourly	27.3	26.2	
3	Frequent: one or more times an hour	11.9	10.9	
4	Almost constant: never free of cough or feeling free of the need to cough	3.5	1.7	
Chest tightness scores				
0	None: unaware of any discomfort	34.7	39.7	0.055
1	Mild: noticeable now and then, but is not bothersome and passes quickly, does not limit activity	29.4	31.7	
2	Moderate: noticeable less than hourly, limits activity and is aggravated or brought on by moderate activity	22.6	21.6	
3	Marked: noticeable one or more times an hour, may be accompanied by dyspnoea, limits activity and is aggravated or brought on by normal activity, such as walking	10.9	10.5	
4	Severe: almost constant, accompanied by dyspnoea, present even when resting and limits all activity	1.7	2.8	
Night-time awakening scores"				
0	Slept through the night	44.7	44.4	0.57
1	Symptoms caused waking once or early awakening	23.9	26.2	
2	Symptoms caused wakening twice or more during the night (including waking early)	21.1	20.4	
3	Symptoms caused wakefulness for most of the night	7.5	6.8	
4	Symptoms so severe that patient did not sleep at all	2.7	2.2	

Data presented as % unless otherwise stated. #: per cent of days during the run-in period in which the indicated score was recorded for patients with and without event-based exacerbations, ": due to respiratory symptoms.

approaches were applied. Patients with event-based exacerbations were subdivided into different groups according to the following. 1) Three groups were subdivided according to the Global Initiative for chronic Obstructive Lung Disease (GOLD) definitions of severity: moderate stage II, severe stage III and very severe stage IV. 2) Three groups were subdivided on the basis of treatment approach, *i.e.* those receiving antibiotics, oral corticosteroids or hospitalisation. These groups included all patients receiving each approach and, therefore, there was some overlap between the groups.

Occurrence of symptoms, rescue medication and PEF in exacerbation-free intervals

The median change in symptoms, rescue medication and morning PEF from baseline to 2 days before an event-defined exacerbation (day 2) was calculated for the exacerbating (event-based) patients. This was compared on a daily basis for all patients to determine what proportion of patients exceeded the median values for each variable. The intention was to determine whether patients with an event-defined exacerbation also exhibited a change in symptoms, rescue

TABLE 2 Symptom algorithms

	Basis	Criteria
Single assessments		
Simple algorithm	Compare the symptom score each day with the score 7 days prior to each day	If an increase in score of ⩾1 is seen for 3 consecutive days
Rescue medication use	Increase in inhalation of rescue medication	One, two or three inhalations more than the number recorded 7 days earlier for 3 consecutive days
Change in PEF	PEF measurement	Drop of 10%, 15% or 20% in morning PEF compared with the 7 days before for 3 consecutive days
Combined symptom scores		
Combined algorithm	Mean of the four symptoms for each day compare each days' mean with that obtained 7 days before	Increase in mean score of ⩾1.0 for 3 consecutive days
Complex algorithm	Mean of the four individual symptom scores, mean of last 3 days compared with same function 1 week earlier	Increase in mean score of at least 0.5, 0.75 or 1.0
Exceeding set mean symptom level	Mean symptom value exceeds a set level for 3 consecutive days	Set level: 1.5, 2.0 or 2.5
Exceeding values from 2-week trial run-in period	Mean symptom level exceeds run-in values for 3 consecutive days	Exceed mean symptom run-in scores by 0.25, 0.5 or 0.75

PEF: Peak expiratory flow.

medication use or morning PEF in the days prior to an event-based exacerbation, thereby identifying any variable that was potentially predictive for an event-based exacerbation.

RESULTS

Of the 796 patients randomised to receive treatment, 468 patients experienced at least one event-based exacerbation, as defined by episodes requiring antibiotics and/or corticosteroids and/or hospital admission (fig. 1). All patients were classified in GOLD stages II-IV. The mean age of these patients was 64.1 yrs and the mean FEV_1 % pred was 36.3. The mean values of symptom scores (minimum 0; maximum 4) at baseline for these patients were as follows: 1) shortness of breath 1.9; 2) cough 1.4; 3) chest tightness 1.2; and 4) night-time awakenings 1.0. The remaining 328 patients had a mean age of 64.1 yrs and a mean FEV_1 % pred of 39.3. The mean symptom scores at baseline were somewhat lower: 1.6, 1.0, 1.3 and 1.0 for the four symptoms, respectively. Table 1 shows the age, FEV_1 % pred and symptoms scores separated into two groups, one experiencing at least one event-based exacerbation and the other with no event-based exacerbation during the study period. There was a statistically significant difference in the symptoms, shortness of breath and cough between the groups (both $p<0.001$).

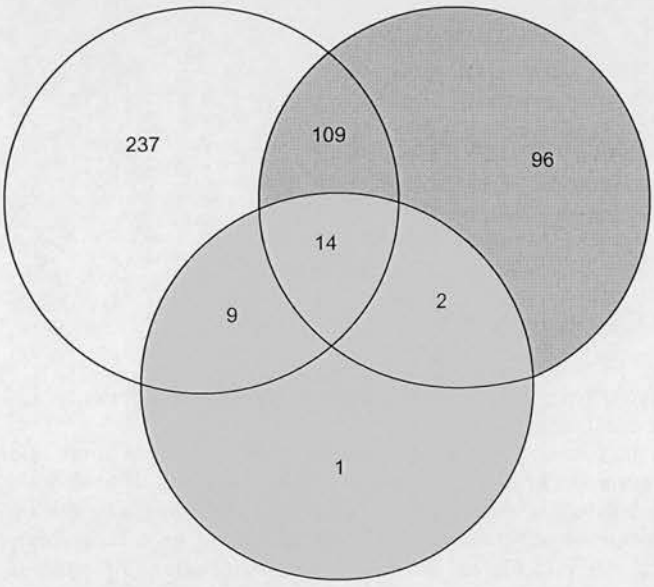

FIGURE 1. Event-based exacerbations. ○: Antibiotics n=369; ●: oral steroids n=219; ●: hospitalisation n=25.

Diary cards were well completed. The available number of records (days with data) averaged 87.8% during the study period (4 weeks after the day of exacerbation).

Population changes

The four individual symptom scores in the days preceding and following the first event-based exacerbation are shown in figure 2. The mean scores for the 468 patients clearly show a similar pattern across all symptoms, increasing steadily in the 2 weeks prior to an exacerbation and returning to baseline values ~2 weeks later. This pattern was seen irrespective of the medication used to treat the exacerbation, with a similar absolute change in symptom score for episodes treated with antibiotics alone or with corticosteroids.

Rescue medication use in the days pre- and post-exacerbation is shown in figure 3. Again, a change was noticed beginning ~2 weeks before an exacerbation, with increasing number of inhalations, and then a slow return to baseline values.

Morning and evening PEF, expressed as a per cent of the predicted values, in the days pre- and post-exacerbation are shown in figure 4. As with the symptom scores, a clear change

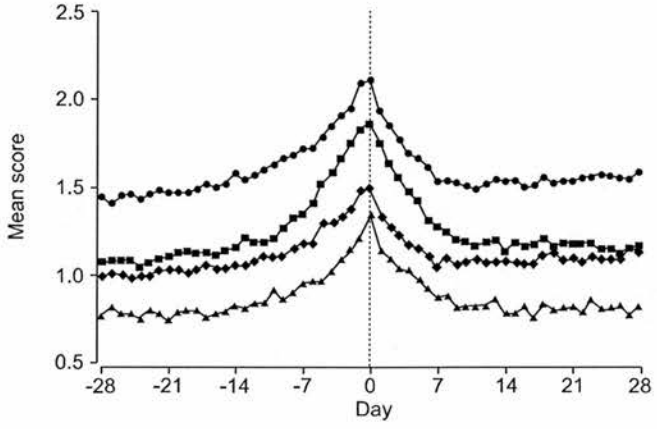

FIGURE 2. Mean values of symptom scores around the first protocol-defined exacerbation. ●: shortness of breath; ■: cough; ◆: chest tightness; ▲: night-time awakening; - - -: day 0, first day of exacerbations.

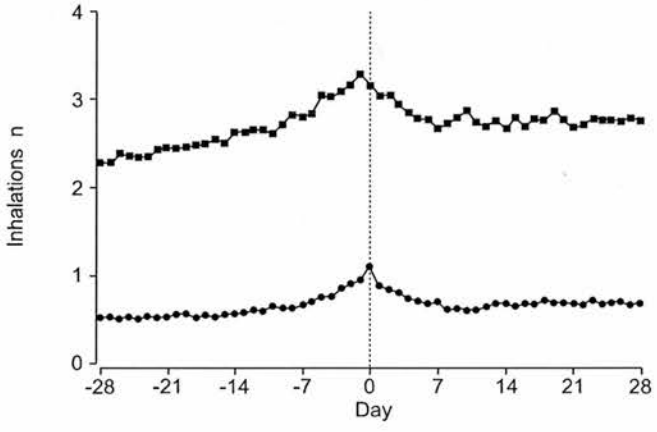

FIGURE 3. Mean values of intake of rescue medication ■: rescue medication (day); ●: rescue medication (night); - - -: day 0, first day of exacerbations.

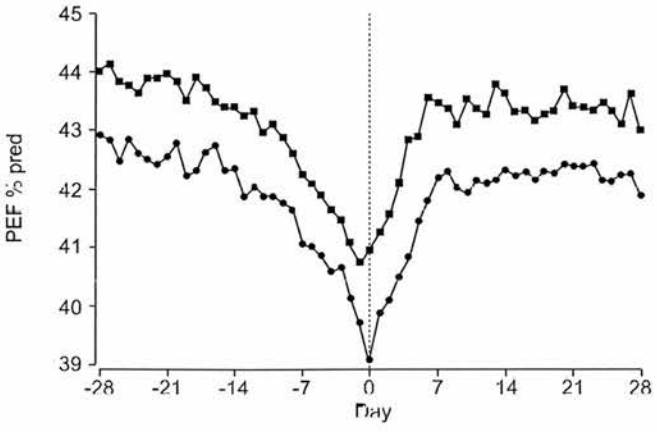

FIGURE 4. Morning peak expiratory flow (PEF) around the first exacerbation. ■: PEF (evening); ●: PEF (morning); - - -: day 0, first day of exacerbation.

in PEF is seen during the exacerbation, with PEF falling steadily (decreases in morning PEF of 9.0% and evening PEF of 7.7% being recorded) in the 2–3 weeks before and returning to baseline values after ~1 week.

Individual changes: simple algorithm, rescue medication and PEF

Simple symptom-based exacerbation calculations

The results of the analyses to identify concurrence between changes in each of the four individual symptoms and event-defined exacerbations are shown in table 3. For breathlessness, 660 out of 796 patients experienced a symptom-based exacerbation, as defined by the simple criteria, and 411 of these 660 patients also experienced an event-based exacerbation. However, only 206 of these 411 exacerbated within 7 days before and after the symptom-based exacerbation occurred, meaning that 44% of the event-based exacerbations were also captured by a change in breathlessness. Assessment of the other three symptoms showed a similar range of concurrence, with the change in cough symptoms occurring in 51.7% of the event-based exacerbations. For all symptoms, varying the time window to 5 and 7 days, or time lag from baseline to 14 and 28 days, had no notable influence on the results.

Increased use of rescue medication

The lowest condition (an increase of one inhalation for 3 consecutive days) was recorded by almost all patients at some time-point during the study (table 3). Approximately half of these were within 7 days of an event-based exacerbation. Restricting the criteria to two or three inhalations resulted in fewer symptom-based exacerbations, but also in a considerably lower percentage of concurrence.

Changes in morning PEF

Assessment of change in morning PEF % pred was only weakly correlated with event-based exacerbations, with even

TABLE 3 Results of analysis of single assessments

	Patients with symptom-based exacerbations	Patients with event-based exacerbations	Concurrence
Individual symptoms			
Breathlessness	660	411	206 (44.0)
Chest tightness	608	382	182 (38.9)
Cough	649	416	242 (51.7)
Night-time awakening	543	353	149 (31.8)
Any symptom	737	451	330 (70.5)
Increased inhalations of rescue medication			
1	672	424	239 (51.1)
2	469	314	130 (27.8)
3	246	183	65 (13.9)
Fall in morning PEF %			
20	235	162	40 (8.6)
15	352	241	63 (13.5)
10	573	373	128 (27.4)

Data presented as n or n (%). PEF: peak expiratory flow.

the smallest change (10%) resulting in only 27.4% concurrence (table 3).

Individual changes: combined symptom scores

Combined algorithm

An arbitrary scale was developed for use in clarifying external rules which would allow definition of an exacerbation objectively or by automated means. The degree of concurrence achieved with this score is shown in table 4, for both a 0.5 and a 0.75 change in combined symptom score (as defined in table 2). A large number of patients met the criteria defining a change in symptom score of ≥ 0.5, but only 224 of these occurred in the time frame considered to be the same event as those described as event-based exacerbations. Increasing the condition to a change in symptom score of 0.75 selected fewer patients, but markedly reduced the degree of concurrence.

Complex symptom-based definition

This represents a moving average for 3 days compared with the average 7 days earlier, the objective being to minimise individual variation (as defined in table 2). A symptom-based criteria of an increase in mean symptom score of 0.5 resulted in almost 60% concurrence (table 4). Changing the criteria to an increase of 0.75 or 1.0 resulted in fewer symptom-based exacerbations and also a lower rate of concurrence.

Symptom mean exceeding a set value

Symptom-based events, defined as a mean symptom value exceeding a 1.5, 2.0 or 2.5 increase for 3 consecutive days, showed a relatively high degree of concurrence at the lower levels (table 4). A symptom-based exacerbation, defined as an increase of 1.5 for 3 days, was seen in almost all patients at some point, 63.3% correlating with an event-based exacerbation. Similar results were seen when symptom-based exacerbations were defined as an increase over the run-in period (table 4).

TABLE 4 Results of analysis of combined symptoms scores

	Patients with symptom-based exacerbations	Patients with event-based exacerbations	Concurrence
Increase in combined symptom score of			
≥ 0.50	639	408	224 (47.9)
≥ 0.75	486	334	154 (32.9)
Increase in mean symptom score of			
≥ 0.50	676	427	279 (59.6)
≥ 0.75	539	303	197 (42.1)
≥ 1.0	387	277	141 (30.1)
Level			
2.5	241	175	105 (22.4)
2.0	399	283	190 (40.6)
1.5	557	366	296 (63.3)
Increase over run-in values			
0.75	319	232	138 (29.5)
0.50	422	291	190 (40.1)
0.25	536	348	247 (52.8)

Data presented as n or n (%).

Effect of COPD severity and therapeutic intervention

Patients with an event-based exacerbation were classified into groups according to the GOLD definitions of severity (very severe stage IV: n=158; severe stage III: n=246; and moderate stage II: n=64) and the pattern of symptoms around the first event-based exacerbation assessed. While the symptom mean was seen to increase markedly in the 7–14 days preceding an event-based exacerbation and decline gradually with resolution, no difference in symptom curve was seen between the three severity groups. Assessment of individual symptoms showed a similar pattern, with only breathlessness separating into three distinct peaks at the point of an event-based exacerbation, with the very severe stage IV patients having the highest degree of breathlessness and the moderate stage II patients the lowest.

There was no significant difference in mean symptom scores if the patients were divided according to treatment (formoterol, budesonide, budesonide/formoterol combination or placebo).

Occurrence of symptoms, rescue medication and PEF in exacerbation-free intervals

As shown in figure 5, an increase in symptoms 2 days prior to an event-defined exacerbation was not seen to be predictive, as a similar proportion of patients had increased levels without resulting in an exacerbation. The same was evident for rescue medication use and PEF levels.

DISCUSSION

Although few clinicians have difficulty in recognising a patient with an exacerbation of COPD, agreeing on a comprehensive

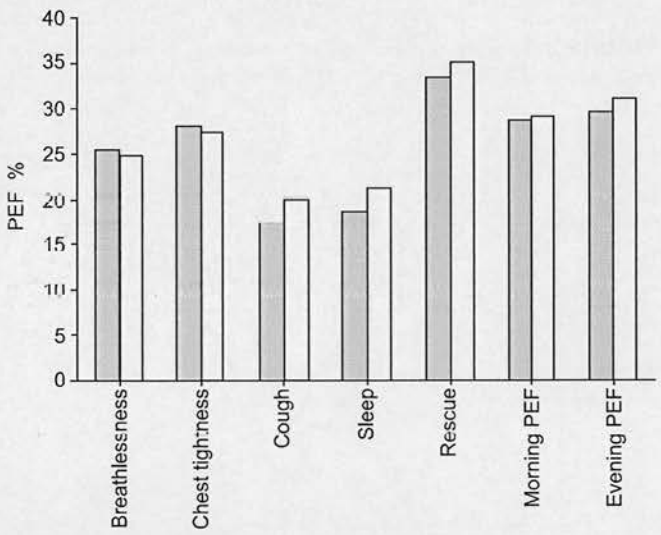

FIGURE 5. Mean percentage of days where symptoms, rescue medication and peak expiratory flow (PEF) exceed the median value for patients with event-based exacerbations 2 days before their first exacerbation. ■: no event-based exacerbation; □: event-based exacerbation.

definition has been surprisingly difficult and is limited by the lack of studies where different approaches to defining an exacerbation have been compared. The present data, relating event-based episodes to changes in symptom intensity, are the first where such a comparison has been possible. Although, on average, symptom intensity peaked around the time therapy was initiated and declined thereafter. Individual symptom-based episodes showed only limited agreement with episodes when the patient sought medical help. Combining the selected symptoms worsened rather than improved the degree of agreement between definitions.

There may be several reasons for this surprising finding. The patients might not have completed their diary cards around the time of an exacerbation (or have reported only one symptom of note). This was not the case as judged by the surprisingly good data completion in the weeks before and after event-based episodes. Retrospective completion of data cannot be excluded in some cases, but given the large number of subjects in different centres it would be surprising if this systematically biased the results.

The population studied was relatively severe, with an event-based exacerbation rate of $1.8 \cdot yr^{-1}$ of those randomised to placebo and $1.4 \cdot yr^{-1}$ in those receiving the budesonide/formoterol combination, in keeping with this severity of disease [21]. All symptoms showed, on average, similar changes around the time of the event-based episodes and rose to a similar degree. An increase in the use of rescue therapy paralleled these changes. The fall in PEF was 4.3% of predicted normal over the course of the event-based episodes, and was very similar to that seen when other symptom-based criteria have been used [22]. However, it was significantly smaller than the current authors' *a priori* threshold used to investigate the value of this criterion. Failure of peak flow to be a reliable pointer to exacerbations in COPD contrasts with the experience in asthma [23] and reflects the importance of increases in lung volumes during such episodes rather than changes in forced expiratory flow [24]. Detecting changes of this magnitude is not practical in individual patients and removes the objective reassurance that PEF data provide when identifying asthma exacerbations.

The baseline spirometric severity was not related to the mean symptom change during the episode. Similar absolute changes in symptoms occurred irrespective of the GOLD stage of disease. However, the baseline level of symptoms did differ with GOLD stage, with breathlessness being scored at a higher level in the initial run-in and during the course of an exacerbation in those in the lower GOLD stages. This may explain why such patients are more likely to seek medical attention when they experience an exacerbation.

The questions selected to monitor with the diary card may have limited the ability to detect all changes of note. This diary card was based on the successful model used in studies of asthma [23] and the present data suggest that it may not be ideal for use in patients with COPD. However, symptoms such as breathlessness were reported in just over 60% of event-based exacerbations, a figure very similar to that seen in exacerbations reported in one centre in London, UK, where a different type of scoring was adopted [25]. Future studies should address the appropriateness of individual questions in identifying exacerbations and, in particular, whether upper respiratory tract symptoms associated with viral infections [26] occur independently of other single symptom combinations. However, a preliminary report in another large study cohort where questions regarding cough and sputum were included may not suggest a better degree of resolution than presented in the current study [27].

Although, several different objective schemes were devised in this study for relating exacerbations identified by a change in therapy to the daily symptom record, the level of agreement was poor. The choice of a graded diary card suggesting specific thresholds to be exceeded may have contributed to this. The approach adopted to identify exacerbations in the on-going COPD cohort studies was reported by the East London group. This requires the patient to note a worsening of the symptom on at least 2 consecutive days, but does not specify by how much symptoms should deteriorate. There is no standardised diary card available at present for use in COPD, although exacerbations can be identified in groups of patients using a simplified breathlessness, cough and sputum score [28]. More work to validate these instruments is clearly needed. Better dating of diary entries using electronic diary cards should reduce some of the noise in the data. However, more information is need about why patients attend their physicians to receive medication and what the doctor is identifying when treatment is initiated. The present data confirm that these processes are not captured simply by an increasing intensity of pre-specified symptoms.

The current data have a number of practical implications. The difficulty in identifying symptoms or PEF change on the diary card makes the introduction of individual self-management plans in COPD difficult, and may explain the limited success of current approaches to this [29]. Although individually limited, the pooled data around the exacerbation indicates that the prodrome may last a little longer than previously suggested [22], with some patients failing to return to baseline symptoms within the 4-week window. The average change in total symptom score was not influenced by the therapy prescribed, suggesting that medication does not change the nature of an event where treatment is sought from the doctor, but does change the number of occasions when this happens.

In conclusion, whether particular aetiologies are more relevant to specific symptom patterns cannot be addressed in trial data such as these. However, the close agreement between the maximal group mean change in symptoms and the onset of therapy does support the use of event-based criteria as a simple reflection of the presence of a clinically important event on average in a chronic obstructive pulmonary disease population. The relationship between initial symptoms and the likelihood of future exacerbation may also help in defining those chronic obstructive pulmonary disease patients where exacerbation prophylaxis is most likely to be helpful.

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Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study

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ABSTRACT: We investigated the impact of season relative to other determinants of chronic obstructive pulmonary disease (COPD) exacerbation frequency in a long-term international study of patients with forced expiratory volume in 1 s (FEV_1) <60% predicted.

COPD exacerbations were defined by worsening symptoms requiring systemic corticosteroids and/or antibiotics (moderate) or hospital admission (severe). Seasonality effect was calculated as the proportion of patients experiencing an exacerbation each month.

Exacerbations in the northern and southern regions showed an almost two-fold increase in the winter months. No seasonal pattern occurred in the tropics. Overall, 38% of exacerbations were treated with antibiotics only, 19% with systemic corticosteroids only and 43% with both, while 20% required hospital admission irrespective of the season. Exacerbation frequency was associated with older age, lower body mass index, lower FEV_1 % pred and history of prior exacerbations. Females and patients with worse baseline breathlessness, assessed using the Medical Research Council (MRC) dyspnoea scale, exacerbated more often (rate ratio (RR) for male *versus* female 0.7, 95% CI 0.7–0.8 ($p<0.001$); RR for MRC dyspnoea score 3 *versus* 1 and 2 combined 1.1, 95% CI 1.1–1.2 ($p<0.001$)). The effect of season was independent of these risk factors.

COPD exacerbations and hospitalisations were more frequent in winter.

KEYWORDS: Chronic obstructive pulmonary disease, exacerbations, mortality, seasonal patterns, TORCH survival study

Patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) experience on average, two to three exacerbation episodes per year [1, 2]. Hospitalisation and COPD-associated mortality account for substantial treatment and healthcare resource utilisation costs [2–4]. COPD exacerbations contribute to a worsening of health-related quality of life over time [1, 2, 5] and their occurrence predicts the likelihood of dying [6].

Factors predicting the frequency and slow resolution of exacerbations include increasing age, more severe airflow obstruction and a history of prior exacerbations [7–10]. These data come from studies of differing size and duration of follow-up that reported annualised exacerbation rates. Less attention has been paid to the influence of time of year on exacerbation occurrence and management. There is evidence of a seasonal variation in the rate of hospital admissions for COPD, with more exacerbations occurring during the winter months compared with summer [11–13]. Exacerbations are also associated with cooler temperatures [14, 15]. This seasonal variation has been reported predominantly in countries in northern regions [16, 17], with little or no similar information available for either the southern regions or the tropics [18–20]. Furthermore, there is a paucity of information about seasonal variation in exacerbation rates and its importance compared with other factors predicting exacerbations. The current analysis was designed to test the impact of seasonal variation on reported exacerbations in relation to other risk factors, using data from the prospective, 3-yr Towards a Revolution in COPD Health (TORCH) study involving 6,112 patients from the northern and southern regions and the tropics [21].

METHODS

Patients

Outpatients aged 40–80 yrs with a diagnosis of COPD, defined in accordance with the European Respiratory Society (ERS) consensus statement [22], who were current or ex-smokers with ⩾10 pack-yrs smoking history were recruited. They had a

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pre-bronchodilator forced expiratory volume in 1 s (FEV1) of <60% of predicted, with reversibility to 400 μg salbutamol of <10% of predicted FEV1 and a FEV1/forced vital capacity ratio of ⩽70% after bronchodilator. Exclusion criteria have been described previously [21] and included long-term oxygen therapy at start of the study, or an exacerbation requiring systemic corticosteroids or hospitalisation during the run-in period.

Study design

TORCH was a multicentre, randomised, double-blind, parallel-group, 3-yr study conducted in 42 countries around the world [21]. Eligible patients were stratified by smoking status and were randomised to receive placebo, 50 μg salmeterol, 500 μg fluticasone propionate or 50/500 μg salmeterol/fluticasone propionate combination *via* the Diskus™/Accuhaler™ inhaler (GlaxoSmithKline, London, UK) (one inhalation twice daily) for 3 yrs. All patients visited the clinic at 12-weekly intervals; during these visits, specific enquiries were made regarding exacerbations or events that required a change in treatment or hospitalisation by asking the standard questions "Have you had any (other) medical problems since your last visit/assessment?" and "Have you taken any new medications, other than those given to you within this study since your last visit/assessment?" Exacerbations were recorded as moderate (defined by worsening symptoms requiring treatment with antibiotics and/or systemic corticosteroids) or severe (defined as those requiring hospitalisation), and were documented by the investigator as an adverse event or serious adverse event. Treatment with short courses of systemic corticosteroids and/or antibiotics as reported by the patient was recorded on the patient's case report form. All patients gave written informed consent, and the study was approved by local ethical review boards and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Statistical analysis

The number of patients reporting a new exacerbation was expressed as a proportion of the patients on treatment during the month in which the exacerbation started. The pattern of exacerbations was analysed according to geographical location, based on the locations of the participating centres. Similar analyses were conducted for all deaths occurring during the 3-yr study period. Study populations were grouped into the northern region (Canada, China, 26 eastern and western European countries, and the USA), the southern region (Argentina, Australia, Brazil, Chile, New Zealand and South Africa) and the tropics (countries lying between the tropics of Capricorn and Cancer: Hong Kong, Malaysia, Mexico, Philippines, Singapore, Taiwan and Thailand).

For seasonal comparisons, in the northern region, we defined summer as June to August inclusive and winter as December to February, with the reverse for the southern region. Recruitment began in September 2000 and the study ended in November 2005. Our investigation of seasonality of exacerbations was restricted to a 4-yr period (April 2001 to March 2005) when sufficient numbers of patients were on treatment to reduce the amount of random variation. For all other analyses, all data were used.

The number of exacerbations experienced by a patient during the study was expressed as a rate per year to account for the differing times on treatment. Exploratory analysis of the association between exacerbation rates during treatment and baseline characteristics was performed by modelling the exacerbation rates using the negative binomial distribution (to account for patient variability), using the logarithm of time on treatment as an offset variable. Smoking status, sex, region, treatment, exacerbations in the year prior to study entry (as recalled retrospectively by the patients or investigators at study entry), body mass index (BMI), Medical Research Council (MRC) dyspnoea score, age and baseline FEV1 % pred were included in the model. Rate ratios (RR) with 95% confidence intervals were calculated for each covariate with all other covariates included in the model.

RESULTS

Demographic and baseline characteristics of the study population are shown in table 1. Mean±SD age was 65±8 yrs and post-bronchodilator FEV1 was 1.23±0.4 L. Males comprised the majority of the study population and >40% of all patients were current smokers. Nearly 60% of patients had at least one exacerbation in the year prior to study entry; half of these had two or more exacerbations.

79% of the study population was recruited from the northern region, 10% from the southern region and 11% from the tropics.

Overall rates of exacerbations

Overall exacerbation rates per year (moderate or severe) are shown in figure 1. The distribution was highly skewed; the majority of patients had between no and two exacerbations per year, but a few had much higher rates. In total, there were ~13,000 exacerbations. The annual rate for moderate or severe exacerbations was 1.13 in the placebo group, 0.97 in the 50 μg salmeterol group, 0.93 in the 500 μg fluticasone propionate group and 0.85 in the 50/500 μg salmeterol/fluticasone propionate group.

Pattern of new exacerbations

In the northern and southern regions, but not the tropics, a seasonal pattern of exacerbations was seen, with a higher proportion of patients exacerbating in the winter months, which was consistent over the 4-yr period. Figure 2a and b shows the raw data of the proportion of patients exacerbating in each month for the northern and southern regions and the tropics, respectively. Figure 2c and d represents the same information averaged into one calendar year. The pattern of exacerbations in the northern region was mirrored by the pattern of exacerbations in the southern region (fig. 2a and c). A higher proportion of patients in the southern region reported an exacerbation in any seasonally adjusted month compared with the northern region (fig. 2c). In the northern region, 5% of patients reported an exacerbation in the summer compared with 9% in the winter, while in the southern region, 7% of patients reported an exacerbation in the summer compared with 12% in the winter (fig. 2c). This seasonal pattern was seen in all four treatment arms.

Management of exacerbations

The proportion of patients with exacerbations treated with systemic corticosteroids alone, antibiotics alone or both in the northern and southern regions is presented in figure 3.

TABLE 1 Patient demographics and baseline characteristics by region

	ITT (efficacy)	Northern	Southern	Tropics
Subjects n	6112	4849	622	641
Age yrs	65.0±8.3	64.8±8.3	65.5±8.5	66.5±7.3
Males %	76	75	72	89
Current smokers %	43	45	36	36
Post-bronchodilator FEV_1 L	1.23±0.4	1.26±0.4	1.16±0.4	1.01±0.4
Post-bronchodilator FEV_1 % pred	44.3±13.4	45.1±13.2	42.4±13.2	40.3±14.3
Reversibility % pred FEV_1	3.7±3.7	3.6±3.8	4.0±3.5	3.5±3.7
BMI $kg \cdot m^{-2}$	25.4±5.2	26.0±5.1	24.6±4.9	21.7±4.1
Exacerbation rate#	1.2±1.6	1.2±1.5	1.2±1.6	1.6±2.3
0 exacerbations %	43	43	42	40
1 exacerbation %	25	25	24	24
⩾2 exacerbations %	32	32	33	36

Data are presented as mean±SD, unless otherwise stated. ITT: intention to treat; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; BMI: body mass index. #: in the 12 months prior to study entry.

Overall, 38% of exacerbations were treated with antibiotics only, 19% with systemic corticosteroids only and 43% with both. In the northern region, more exacerbations in the winter (43%) were treated with antibiotics compared with those in the summer (37%). This pattern was reversed for exacerbations treated with systemic corticosteroids (15% in winter but 24% in summer). A clear seasonal treatment pattern was not seen in the southern region, possibly due to the smaller number of patients.

The proportion of all patients who required hospitalisation for exacerbation in any given month was higher in the winter. For instance, in the northern region, the highest proportion, in December (1.9%), was double that reported in the lowest month (August; 0.9%). However, the proportion of exacerbations requiring hospitalisation was similar year-round, with a summer mean of 18.3% and a winter mean of 18.8%. This pattern was similar in the southern region, but different in the tropics, with a higher proportion of events requiring hospitalisation (31.2%) than in the other regions (18.3% in the northern region and 15.7% in the southern region). Across all regions 20% of exacerbations required hospitalisation.

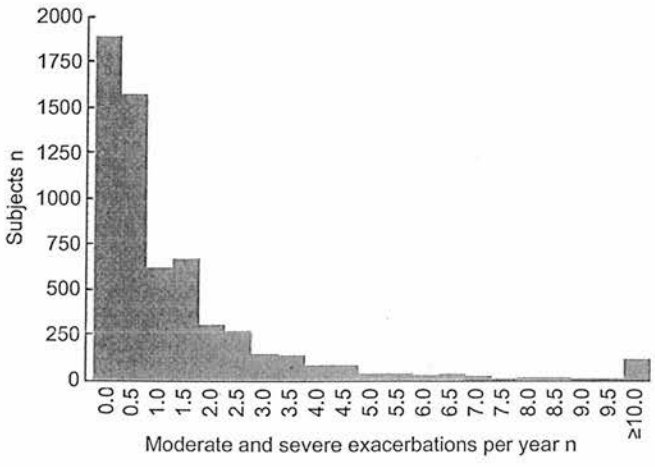

FIGURE 1. Distribution of exacerbation rates per patient per year during the study. The very high calculated exacerbation rates (⩾10) were primarily due to premature drop-out of frequent exacerbators with <6 months follow-up time.

Factors affecting exacerbation rates

The effect of covariates on the rate of exacerbations during the study is shown in table 2. Season was a significant covariate with respect to exacerbation rate. In northern and southern regions, there were more exacerbations in the winter compared with the summer. Patients ⩾75 yrs of age, compared with patients <55 yrs of age, had 20% more exacerbations (RR 1.2, 95% CI 1.0–1.3; p=0.023). Compared with patients with a mean BMI of 20 to <25 $kg \cdot m^{-2}$ at baseline, patients with a BMI of ⩾29 $kg \cdot m^{-2}$ had 10% fewer exacerbations (RR 0.9, 95% CI 0.8–0.9; p<0.001), while a low BMI (<20 $kg \cdot m^{-2}$) was associated with a 10% increased rate of exacerbations (RR 1.1, 95% CI 1.0–1.2; p=0.241).

Low FEV_1 was also associated with an increased rate of exacerbation (FEV_1 <30 compared with ⩾50% pred: RR 1.9, 95% CI 1.7–2.1; p<0.001). Patients who reported one exacerbation in the year prior to study entry had a 50% higher rate of exacerbations while on treatment (RR 1.5, 95% CI 1.4–1.6; p<0.001) and those reporting two or more exacerbations in the year prior to study entry had nearly double the rate (RR 1.9, 95% CI 1.8–2.1; p<0.001) compared with patients who reported no exacerbations.

Males had a 30% lower exacerbation rate than females (RR 0.7, 95% CI 0.7–0.8; p<0.001). Increasing severity of dyspnoea, based on baseline MRC dyspnoea grade, was associated with a greater rate of exacerbations, a grade of 3 having an exacerbation RR of 1.1 (95% CI 1.1–1.2; p<0.001) and grades 4 and 5 having a RR of 1.3 (95% CI 1.2–1.4; p<0.001), compared with grades 1 and 2.

Current smoking was associated with a 10% lower rate of reported exacerbations than former smoking (0.9 RR, 95% CI 0.8–0.9; p<0.001), after adjusting for other covariates.

The reporting of exacerbations differed according to region, with the rate in the northern region being 20% lower than in the southern region (RR 0.8, 95% CI 0.7–0.9; p<0.001).

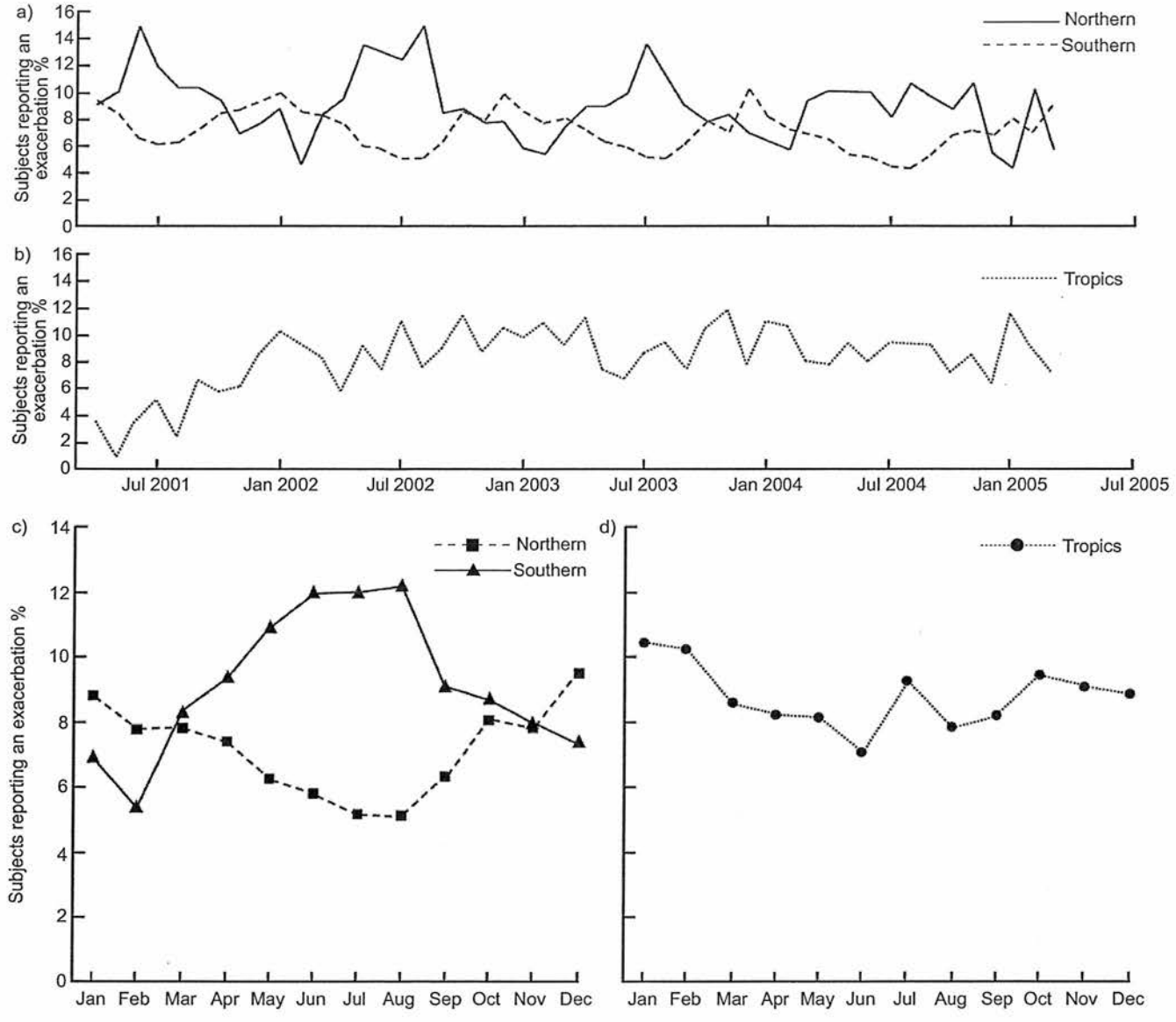

FIGURE 2. Proportion of patients reporting an exacerbation in the a) northern and southern regions and b) tropics over 4 yrs, and reporting an exacerbation in the c) northern and southern regions and d) tropics averaged over one calendar year.

The seasonal influence on exacerbation pattern was evident in all the patient subgroups studied. This is illustrated in figure 4 for FEV1 % pred and MRC dyspnoea grade.

Mortality

There were more deaths in the 3 months of winter than the 3 months of summer. In the northern region, 625 of the 4,849 patients died and 180 (29%) of these deaths occurred during the 3 months of winter in the 3-yr study period, while 135 (22%) occurred in the summer. In the southern region 113 of the 622 patients died, 42 (37%) during winter compared with 16 (14%) during the summer.

These differences in seasonal mortality were more evident for COPD-related deaths, which accounted for 41% of all deaths in TORCH. In the northern region, 79 (34%) of the 235 COPD-related deaths occurred during winter while 48 (20%) occurred in the summer. In the southern region, 27 (55%) of these deaths occurred during winter and four (8%) during the summer.

DISCUSSION

COPD patients and their doctors know that exacerbations occur commonly in the winter months, but data to establish the size of this effect have been lacking. Exacerbations defined by healthcare use, as proposed recently by the American Thoracic Society (ATS)/ERS task force [23], were more common during winter. These patterns were consistent from year to year over the study period and accounted for an almost two-fold increased risk of exacerbation in winter, in northern and southern region countries, but not in the tropical countries.

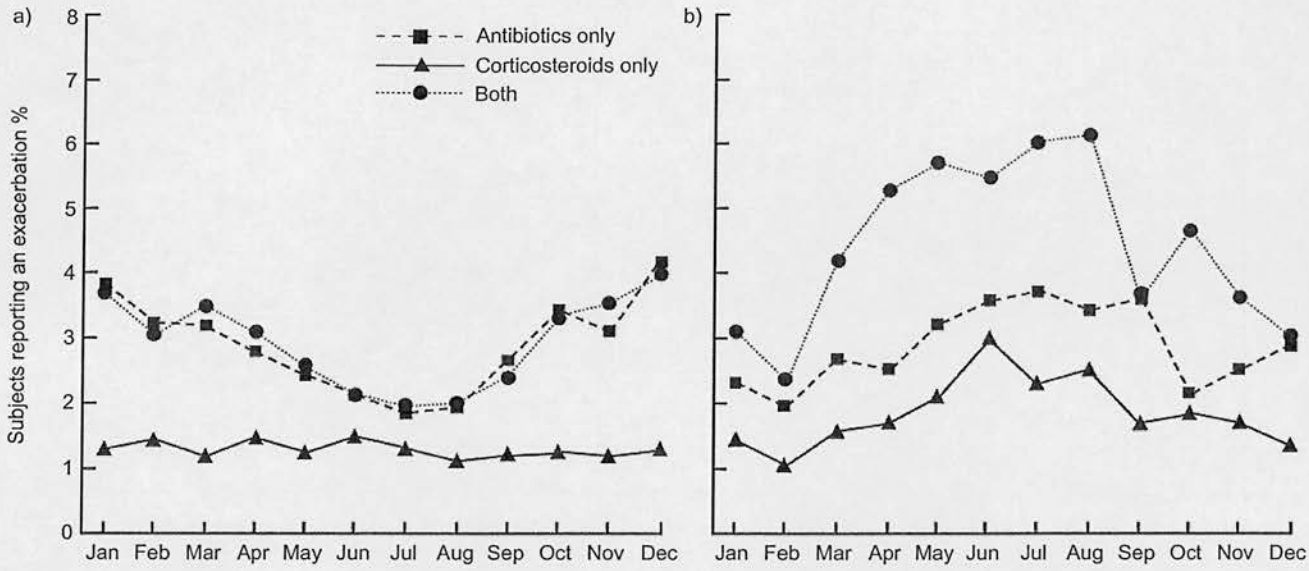

FIGURE 3. Proportion of patients reporting an exacerbation and treatment received in the a) northern and b) southern regions.

TABLE 2 Effect of covariates on the rate of moderate and severe exacerbations

Factor	RR (95% CI)	p-value
Smoking status		
Current *versus* former	0.9 (0.8–0.9)	<0.001
Age yrs		0.064
55–64 *versus* <55	1.1 (1.0–1.3)	0.012
65–74 *versus* <55	1.1 (1.0–1.3)	0.020
⩾75 *versus* <55	1.2 (1.0–1.3)	0.023
Post-bronchodilator FEV1 % pred		<0.001
<30% *versus* ⩾50%	1.9 (1.7–2.1)	<0.001
30 to <50% *versus* ⩾50%	1.4 (1.3–1.5)	<0.001
Sex		
Male *versus* female	0.7 (0.7–0.8)	<0.001
COPD exacerbations in the previous year		<0.001
1 *versus* 0	1.5 (1.4–1.6)	<0.001
⩾2 *versus* 0	1.9 (1.8–2.1)	<0.001
BMI kg·m^{-2}		<0.001
<20 *versus* 20 to <25	1.1 (1.0–1.2)	0.241
25 to <29 *versus* 20 to <25	1.0 (0.9–1.0)	0.262
⩾29 *versus* 20 to <25	0.9 (0.8–0.9)	<0.001
MRC dyspnoea grade		<0.001
3 *versus* 1+2	1.1 (1.1–1.2)	<0.001
4+5 *versus* 1+2	1.3 (1.2–1.4)	<0.001
Region		<0.001
North *versus* south	0.8 (0.7–0.9)	<0.001
Tropics *versus* south	0.9 (0.8–1.0)	0.045

Rate ratios (RR) with 95% confidence intervals were calculated for each covariate with all other covariates included in the model. Multivariate negative binomial model (each variable adjusted for all the others). FEV1: forced expiratory volume in 1 s; % pred: % predicted; COPD: chronic obstructive pulmonary disease; BMI: body mass index; MRC: Medical Research Council.

Thus far, data supporting a seasonal pattern in COPD exacerbations have been derived from smaller studies conducted mainly in Europe [12–14, 16, 17], where a seasonal effect has been reported as part of other analyses. The TORCH study population comprises data collected over 3 yrs from patients in 42 countries and, as such, provides sufficient power to extend and support the previously reported findings. COPD hospital admissions and deaths increase dramatically in the winter months, as do general practice visits for respiratory tract infections [14–17]. Factors potentially contributing to this include increased exposure to viral infections, increased host susceptibility, greater time spent indoors, reduced physical activity and temperature-related reduction in lung function. These patterns also relate to lower weekly mean temperatures, as well as influenza activity and personal cold exposure factors [24]. The mechanisms by which a greater risk of respiratory infections occurs in winter are complex, and include the interaction of temperature and humidity, changes in human behaviour, exposure to colder air indoors and outdoors [14–17, 25–28], air pollution, and greater vulnerability of the local host defence [20, 29].

The seasonal variation was not seen in tropical countries that are characterised by relatively constant temperatures, with a mean of ⩾18°C (⩾64°F), all year round. In tropical regions, there is background influenza activity throughout the year [30, 31], which may contribute to a more stable pattern of exacerbations throughout the year, as noted in the present study. Seasonal variations occur with some infections in the tropics, but may be more closely related to the wet season, air pressure and relative humidity rather than temperature alone [17, 18, 20]. Other factors include outdoor pollution [30–32] and its interaction with cooler temperatures. The tropical countries in TORCH differ in distance from the equator and meteorological characteristics, which produce different seasonal patterns of respiratory illness between countries [33].

The seasonal variation in the number of exacerbation events was accompanied by a variation in the treatment of exacerbations.

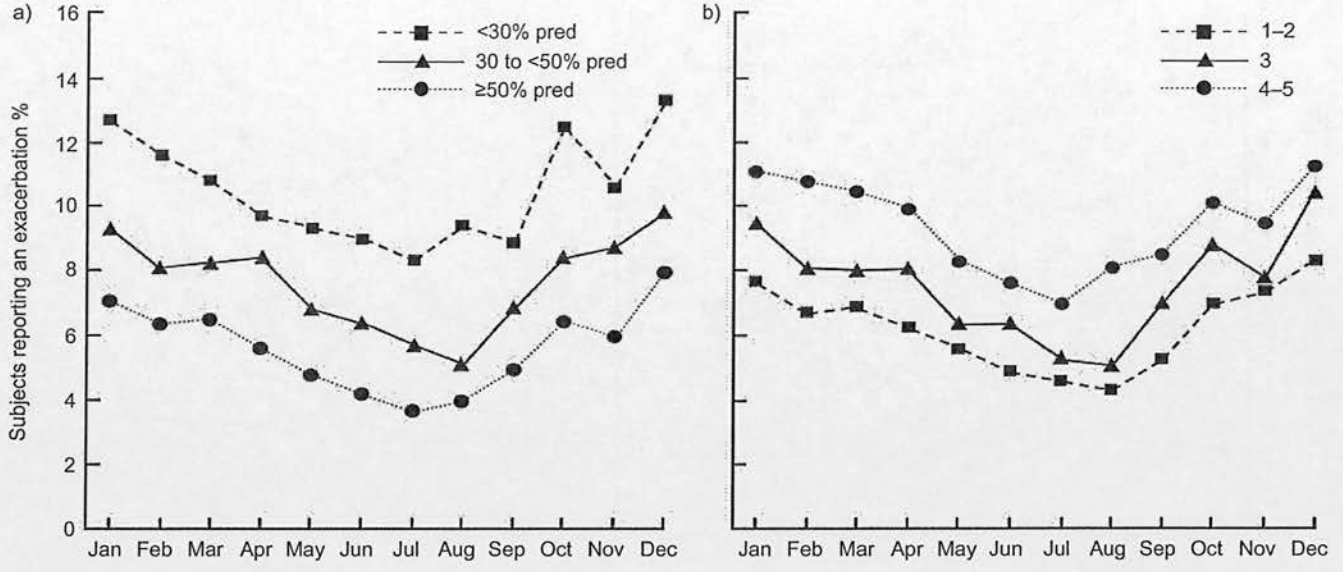

FIGURE 4. Proportion of patients reporting an exacerbation in the northern region by a) forced expiratory volume in 1 s and b) Medical Research Council dyspnoea grade. % pred: % predicted.

Antibiotics were used alone or in combination with steroids more frequently in the winter months compared with summer in the northern region. The treatment difference may reflect differences in the way exacerbation patients present in the winter, but data about seasonal variation in the microbiology of COPD patients are lacking. In contrast, in the southern region, both antibiotic and systemic corticosteroid use increased in the winter, and there was a strong tendency for both to be used in combination. The reason for these differences cannot be determined here and requires further study.

More patients were hospitalised due to COPD in the winter months, although, in absolute terms, the proportion of cases where this occurred was low. However almost 20% of exacerbations in our large, worldwide population required hospitalisation, and this was consistent between the seasons and very similar to that reported in a smaller US study [34]. Moreover, the relative proportion of events leading to hospital admission was unaffected by season, suggesting that the colder weather increased the number, rather than the overall severity, of exacerbations.

Like other researchers, we found that older age, having a lower BMI, a lower FEV1 and a higher incidence of exacerbations in the previous year all significantly increased the risk of exacerbations [7–10]. In addition, we found that sex and MRC dyspnoea grade at study entry, and smoking status are risk factors. Females report more breathlessness for similar levels of airflow obstruction and are more likely to receive treatment for COPD than males [35, 36]. They may, therefore, be more likely to be classified as having an exacerbation. However, there are also data indicating that females are at higher risk of being hospitalised for exacerbations [37], which is unlikely to be due solely to differential symptom reporting. A higher MRC dyspnoea grade may identify patients more likely to receive exacerbation treatment when they present with worsening symptoms. However, MRC grade also relates to exercise performance and the degree of activity normally undertaken is a predictor of the risk of exacerbation [7, 38]. The paradoxical observation that current smokers were less likely to exacerbate than ex-smokers may not be a chance finding. Potential explanations may be a healthy survivor effect or the possible beneficial effect of smoking on sputum clearance [39, 40].

Our data differ in the magnitude of some of the associations from those reported by HURST *et al.* [10] for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points (ECLIPSE) study. We identified almost twice as many exacerbations as that observational study, which included more patients with moderate COPD, who were taking more medication than in our clinical patient population. Moreover, our study was not confined to Europe, North America and New Zealand and, unlike ECLIPSE, we did not record the presence of reflux symptoms. While these factors help explain some of the differences in predictive capacity, it is reassuring to see the considerable agreement in the determinants of exacerbation risk, irrespective of the composition of the study population. Notably, the seasonal effect on exacerbations occurred independently of all the identified risk factors.

Winter mortality from pre-existing respiratory disease was the single strongest predictor of excess deaths in a large general practice-based UK study [41] and pre-existing respiratory disease increased mortality from cardiovascular but not respiratory causes. Several other studies have demonstrated excess all-cause, cardiovascular and respiratory mortality in winter, which is greater in females than males [25–27]. Somewhat paradoxically, vulnerability to death is increased to a greater extent for a given fall of temperature in regions with warmer winter temperatures. This appears to relate to greater personal cold exposure, lack of indoor heating, failure to dress appropriately for the cold and reduced outdoor physical activity [27, 28]. In our population, possibly due to the limited number of events, especially in the southern region, we did not see a clear seasonal pattern in mortality.

There are strengths and limitations of our data. We recorded data in a standardised way in a large patient population and carefully identified the time and cause of death [42]. This approach provided adequate statistical power to test for differences due to region or risk factors. Although we excluded subjects with known serious comorbidities, including those dependent on oxygen therapy at entry, we do not believe the study population and setting bias our main findings. We recognise that ours was a treatment intervention trial and not an epidemiological study, and acknowledge the inherent differences between these two study types. However, the lack of interaction between any of the treatments used in this study and the factors identified as predicting exacerbation allowed us to pool all the data for this analysis, enabling analysis from >6,000 patients.

Conclusion

In the TORCH trial, the major burden of exacerbations fell in the winter months of both northern and southern regions of the world, which aligns with the perceptions of COPD patients and their doctors. Furthermore, the risk factors identified in this study (which, it must be considered, was an interventional study) may make it possible to prospectively profile an individual's risk of exacerbating and, thus, allow optimisation of care to reduce this risk. Further studies to establish the feasibility of such an approach are warranted.

SUPPORT STATEMENT

This study was funded by GlaxoSmithKline (study code SCO30003).

CLINICAL TRIAL

This study is registered at www.clinicaltrials.gov with identifier number NCT00268216.

STATEMENT OF INTEREST

Statements of interest for all authors and for the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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ORIGINAL ARTICLE

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND

Although we know that exacerbations are key events in chronic obstructive pulmonary disease (COPD), our understanding of their frequency, determinants, and effects is incomplete. In a large observational cohort, we tested the hypothesis that there is a frequent-exacerbation phenotype of COPD that is independent of disease severity.

METHODS

We analyzed the frequency and associations of exacerbation in 2138 patients enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study. Exacerbations were defined as events that led a care provider to prescribe antibiotics or corticosteroids (or both) or that led to hospitalization (severe exacerbations). Exacerbation frequency was observed over a period of 3 years.

RESULTS

Exacerbations became more frequent (and more severe) as the severity of COPD increased; exacerbation rates in the first year of follow-up were 0.85 per person for patients with stage 2 COPD (with stage defined in accordance with Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages), 1.34 for patients with stage 3, and 2.00 for patients with stage 4. Overall, 22% of patients with stage 2 disease, 33% with stage 3, and 47% with stage 4 had frequent exacerbations (two or more in the first year of follow-up). The single best predictor of exacerbations, across all GOLD stages, was a history of exacerbations. The frequent-exacerbation phenotype appeared to be relatively stable over a period of 3 years and could be predicted on the basis of the patient's recall of previous treated events. In addition to its association with more severe disease and prior exacerbations, the phenotype was independently associated with a history of gastroesophageal reflux or heartburn, poorer quality of life, and elevated white-cell count.

CONCLUSIONS

Although exacerbations become more frequent and more severe as COPD progresses, the rate at which they occur appears to reflect an independent susceptibility phenotype. This has implications for the targeting of exacerbation-prevention strategies across the spectrum of disease severity. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT00292552.)

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THE NATURAL HISTORY OF CHRONIC OBstructive pulmonary disease (COPD) is punctuated by exacerbations — acute worsening of symptoms. Exacerbations appear to accelerate the decline in lung function that characterizes COPD,[1,2] resulting in reduced physical activity,[3] poorer quality of life,[4] and an increased risk of death,[5] and they are also responsible for a large proportion of the health care costs attributable to this prevalent condition.[6] Consequently, exacerbations are important outcomes in clinical trials, and their prevention is a key component of COPD-management strategies.[7]

Despite the importance of exacerbations, we know relatively little about their incidence, their determinants, and their effects in patients with COPD at various levels of severity. Although exacerbations are generally considered to become more frequent as the severity of the underlying COPD increases, the most reliable predictor of exacerbations in an individual patient appears to be a history of exacerbations.[8] There may therefore be a phenotype of exacerbation susceptibility that includes milder forms of COPD. However, this theory has not been adequately investigated because our current understanding of COPD exacerbations and their relationship to disease severity is based on large intervention studies[9,10] or multiple smaller studies that have used varying definitions of exacerbation.[8] We used data from a large observational study to test the hypothesis that there is a frequent-exacerbation phenotype of COPD that is independent of disease severity.

METHODS

STUDY DESIGN AND PATIENTS

This analysis was based on data collected as part of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) observational study.[11] The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent, and the study was approved by the relevant ethics and review boards.

The recruitment criteria included an age of 40 to 75 years, a history of 10 or more pack-years of smoking, a forced expiratory volume in 1 second (FEV_1) of less than 80% of predicted value after bronchodilator use, and a ratio of FEV_1 to forced vital capacity (FVC) of 0.7 or less after bronchodilator use.

At baseline, patients underwent standard spirometry after the administration of 400 μg of inhaled albuterol. Computed tomographic (CT) scanning of the chest was performed to evaluate the severity and distribution of emphysema (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). The condition of the patients was graded according to the stages of disease defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[12] After the baseline visit, patients were followed for a total of seven visits: at 3 months, at 6 months, and every 6 months thereafter for 3 years.

The patients' self-reported respiratory symptoms, medications, smoking history, occupational exposure, and coexisting medical conditions were documented at study entry with the use of the well-established American Thoracic Society–Division of Lung Disease (ATS-DLD) questionnaire, which was updated for the purpose of this study.[13]

Serum and plasma samples were stored at −80°C until they were analyzed. Details of the assays are described in the Supplementary Appendix. Any samples with values below the lower limit of quantification were assigned a value that was half of the lower limit.

A detailed description of methods can be found in the Supplementary Appendix. The study was conducted in accordance with the protocol, which is available at NEJM.org.

STUDY OUTCOMES

Exacerbations were a critical outcome. The case definition of an exacerbation was a functional one, based on the decision by a patient's primary clinician or by study personnel to prescribe antibiotics or systemic corticosteroids, alone or in combination. Primary clinicians were not given a specific list of criteria that had to be met for an event to be classified as an exacerbation, but they were instructed to base their decision on common clinical criteria. This case definition therefore met the criteria for a definition of health care utilization, and the exacerbations we recorded would be classified as moderate or severe in intensity.[14] The case definition remained the same during the 3 years of active data accrual, and identical criteria were applied retrospectively when we collected data from patients on the number of exacerbations they had had in the year before study enrollment.

Patient-reported measures at study entry included assessments of dyspnea (made with the use of a modified Medical Research Council dyspnea

Table 1. Characteristics of the Patients According to the Severity of COPD.*

Characteristic	All Patients (N=2138)	Moderate — GOLD Stage 2 (N=945)	Severe — GOLD Stage 3 (N=900)	Very Severe — GOLD Stage 4 (N=293)	P Value
Age (yr)	63±7	63±7	64±7	62±7	0.03
Female sex (%)	35	40	32	26	<0.001
Current smoker (%)	36	38	37	28	0.016
Body-mass index†	27±6	27±6	26±6	25±6	<0.001
FEV_1 after bronchodilator use (liters)	1.35±0.52	1.75±0.45	1.13±0.27	0.72±0.16	<0.001
FEV_1 after bronchodilator use (% of predicted value)	48±16	63±8	40±6	25±4	<0.001
FEV_1:FVC (%)	45±12	53±9	40±9	32±8	<0.001
Distance walked in 6 min (m)	370±121	406±112	357±117	290±119	<0.001
BODE index‡	3.2±2.1	1.6±1.4	4.0±1.6	5.7±1.6	<0.001
Emphysema					<0.001
Low attenuation areas (no.)	18±12	12±10	20±12	28±13	<0.001
Extent >5% of total area (%)§	75	63	82	92	<0.001
Patient-reported outcomes‡					
MRC dyspnea score ≥2 (%)	53	40	59	80	<0.001
CES depression score	11±9	11±9	12±9	13±10	0.002
FACIT fatigue score	35±11	37±10	34±11	32±11	<0.001
SGRQ for COPD, total score	50±20	42±21	54±18	62±16	<0.001
Medication for COPD (%)¶					
Any long-acting bronchodilator	76	67	83	86	<0.001
Any inhaled corticosteroid	72	60	80	86	<0.001
Any methylxanthine	14	9	16	20	<0.001
Any leukotriene antagonist	3	3	4	3	0.51
Exacerbations					
≥1 in preceding yr (%)	47	39	52	62	<0.001
≥2 in study yr 1 (%)	29	22	33	47	<0.001
Rate in yr 1 (no./patient)	1.21	0.85	1.34	2.00	<0.001
Requiring hospitalization	0.22	0.11	0.25	0.54	<0.001
Requiring oral corticosteroids only	0.14	0.10	0.15	0.21	<0.001
Requiring antibiotics only	0.44	0.37	0.46	0.60	<0.001
Requiring corticosteroids and antibiotics	0.41	0.27	0.47	0.65	<0.001

* Plus–minus values are means ±SD unless otherwise noted. The table includes data for the 56 patients who died (from any cause) during year 1 of the study; 16 had GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 2 COPD, 26 had GOLD stage 3, and 14 had GOLD stage 4. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The BODE index takes into account body-mass index, airway obstruction (as assessed on the basis of FEV_1), dyspnea (as measured with the Medical Research Council [MRC] dyspnea scale), and exercise tolerance (as measured by a 6-minute walk test); scores range from 0 to 10. The Center for Epidemiologic Studies (CES) depression scale ranges from 0 to 60, with higher scores indicating more severe depression. The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale ranges from 0 (most severe fatigue) to 52 (least severe fatigue). Scores on the St. George's Respiratory Questionnaire (SGRQ) range from 0 (good health status) to 100 (poor health status). The MRC dyspnea scale ranges from 0 (no dyspnea) to 4 (indicating that the patient is too breathless to leave home or becomes breathless when dressing or undressing) (a score of 4 indicates a minimally important clinical difference).

§ The extent of disease was evaluated by a radiologist.

¶ Information on medication was self-reported; patients may have been taking more than one medication.

scale[15]), quality of life (St. George's Respiratory Questionnaire for patients with COPD[16]), fatigue (Functional Assessment of Chronic Illness Therapy fatigue scale[17]), and depression (Center for Epidemiologic Studies depression scale[18]).

STATISTICAL ANALYSIS

Descriptive data are reported as means ±SD or percentages, as appropriate. Comparisons between groups for descriptive summaries were performed with the use of analysis of variance. The incidence of exacerbations was summarized as a per-person per-year rate. Differences in exacerbations between groups were analyzed with the use of a nonparametric Kruskal–Wallis test. In the initial exploration of data, exacerbations were analyzed as an indicator variable (a patient did have or did not have an exacerbation during year 1) fitting univariate models with the use of logistic regression.

Multinomial logistic regression was performed with the use of PROC CATMOD in SAS, with the frequency of exacerbations during year 1 classified as none, one, or two or more to more fully characterize the associations between selected baseline factors and exacerbation frequency. We defined frequent exacerbations as two or more exacerbations in a year because this definition coincides with current health care utilization criteria for frequent exacerbations. For the multivariate analyses, a stepwise approach was used. All variables that were explored in the univariate analyses were considered in the multivariate model, with age, sex, smoking status, and body-mass index included as covariates in all models. A conservative significance threshold of 0.01 was used to determine the qualification of data for entry into or deletion from the model. All reported P values are nominal and two-sided and were not adjusted for multiple comparisons. Stepwise logistic regression was used for analyses involving patients with very severe COPD (GOLD stage 4). Biomarker data were $\log_{10}$-transformed before all regression analyses. All patients who underwent at least 30 days of follow-up were included in the regression analyses.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 2164 patients were recruited for the study, and 2138 patients were enrolled and observed during follow-up. The baseline characteristics of the patients are reported in Table 1, categorized according to the severity of COPD. As the severity increased, exacerbations were both more frequent and more severe (Fig. 1). In the first year of follow-up, the exacerbation rates were 0.85 per person for patients with moderate disease (GOLD stage 2), 1.34 for those with severe disease (GOLD stage 3), and 2.00 for those with very severe disease (GOLD stage 4). The severity of disease also affected hospitalization in year 1, with the proportion of patients who were hospitalized increasing with the severity of disease: GOLD stage 2, 7%; GOLD stage 3, 18%; and GOLD stage 4, 33%.

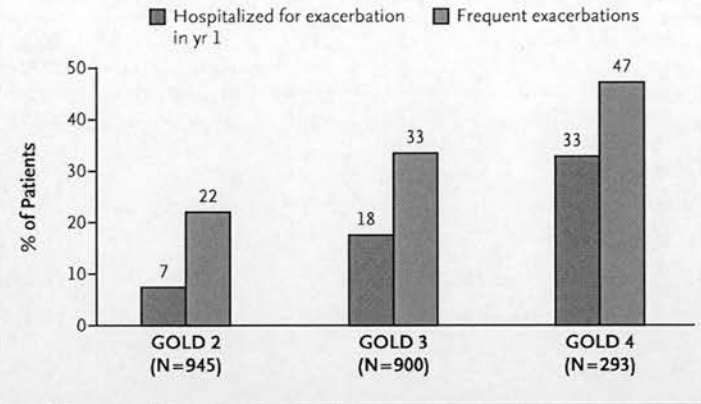

Figure 1. Association of Disease Severity with the Frequency and Severity of Exacerbations during the First Year of Follow-up in Patients with Chronic Obstructive Pulmonary Disease.

Patients with two or more exacerbations during the year were considered to have frequent exacerbations. An exacerbation requiring hospitalization was classified as severe. Disease severity was classified according to the stages of disease defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). P<0.001 for both comparisons.

FACTORS ASSOCIATED WITH EXACERBATIONS

In univariate logistic-regression analysis, we assessed factors associated with at least one exacerbation during the first year of follow-up, using all available baseline assessments in the whole cohort. The best predictor of an exacerbation in the first year was a treated exacerbation in the year before study entry (odds ratio, 4.30; 95% confidence interval [CI], 3.58 to 5.17; P<0.001). Other variables significantly associated with exacerbations are shown in Table 2.

Factors that were independently associated with exacerbations during the first year of follow-up, on the basis of a multinomial regression model,

Table 2. Univariate Associations with the Occurrence of Exacerbations during the First Year of Follow-up.*

Baseline Characteristics	Odds Ratio (95% Wald CI)	P Value
Demographic and clinical characteristics		
Self-reported exacerbation during preceding yr — yes vs. no	4.30 (3.58–5.17)	<0.001
BODE index — per increase of 1 point	1.23 (1.18–1.28)	<0.001
MRC dyspnea score — 2, 3, or 4 vs. 0 or 1	1.83 (1.54–2.18)	<0.001
Distance walked in 6 min — per decrease of 50 m	1.12 (1.08–1.16)	<0.001
Post-secondary (or higher) education level — yes vs. no	0.70 (0.58–0.83)	<0.001
Fat-free mass index — per increase of 1 point	0.93 (0.90–0.97)	<0.001
Sex — female vs. male	1.42 (1.19–1.71)	<0.001
Body-mass index — per increase of 1 point	0.98 (0.97–1.00)	0.03
Age — per 10-year increase	1.14 (1.01–1.28)	0.04
Smoking status — current vs. former smoker	0.83 (0.70–0.99)	0.04
Lung function		
FEV_1 — per 100-ml decrease	1.11 (1.10–1.14)	<0.001
FEV_1 — per 5% decrease in % of predicted value	1.15 (1.11–1.18)	<0.001
GOLD stage — per increase to next stage	1.74 (1.53–1.97)	<0.001
FEV_1:FVC — per 1% decrease	1.03 (1.02–1.04)	<0.001
FVC — per 100-ml decrease	1.04 (1.03–1.05)	<0.001
Emphysema		
Per 5% increase in low-attenuation areas	1.16 (1.11–1.20)	<0.001
Radiologic score >5% — yes vs. no	1.79 (1.45–2.21)	<0.001
Patient-reported outcomes		
SGRQ score for COPD — per 4-point worsening	1.10 (1.08–1.12)	<0.001
FACIT score for fatigue — per 1-point worsening	1.03 (1.02–1.04)	<0.001
CES score for depression — per 1-point worsening	1.03 (1.02–1.04)	<0.001
Laboratory values		
Platelet count — per increase of $10\times10^3/mm^3$	1.02 (1.01–1.04)	<0.001
White-cell count — per increase of $1\times10^3/mm^3$	1.07 (1.03–1.12)	<0.001
Neutrophil count — per increase of $1\times10^3/mm^3$	1.02 (1.01–1.03)	<0.001
Biomarkers†		
Fibrinogen — mg/dl	1.35 (1.22–1.49)	<0.001
High-sensitivity C-reactive protein — mg/liter	1.24 (1.13–1.37)	<0.001
Chemokine ligand 18 — ng/ml	1.13 (1.02–1.25)	0.02
Surfactant protein D — ng/ml	1.10 (1.01–1.20)	0.04
Self-reported symptoms and disease history — yes vs. no‡		
Gastroesophageal reflux or heartburn	1.69 (1.38–2.06)	<0.001
Wheezing	1.56 (1.31–1.86)	<0.001
Osteoporosis	1.74 (1.34–2.27)	<0.001
Asthma	1.52 (1.23–1.87)	<0.001
Chronic cough	1.20 (1.01–1.42)	0.04

* The full version of this table, including all baseline characteristics, is available in the Supplementary Appendix. Only significant variables are listed. Nonsignificant variables included other clinical data (number of pack-years of smoking), other laboratory values (percentage of blood eosinophils and hemoglobin), other biomarker data (interleukin-6, interleukin-8, Clara cell protein-16, and tumor necrosis factor α), and other data on self-reported symptoms and disease history (hypertension, hay fever, chronic bronchitis or chronic phlegm production, "lung trouble" before 16 years of age, exposure to chemical fumes or dusts at work, and cardiovascular and sinus disease). BODE denotes body-mass index, (airway) obstruction, dyspnea, and exercise tolerance; CES Center for Epidemiologic Studies; FACIT Functional Assessment of Chronic Illness Therapy; FEV_1 forced expiratory volume in 1 second; FVC forced vital capacity; GOLD Global Initiative for Chronic Obstructive Lung Disease; MRC Medical Research Council; and SGRQ St. George's Respiratory Questionnaire.

† The increment for biomarker changes was 1 SD on the log scale.

‡ Data on self-reported history are based on subjects' responses to the ATS-DLD questionnaire.

Table 3. Factors Associated with Increased Exacerbation Frequency in the Stepwise Multivariate Model.*

Factor	Number of Exacerbations						P Value for Overall Model
	≥2 vs. 0		1 vs. 0		≥2 vs. 1		
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*	*odds ratio (95% CI)*	*P value*	
Exacerbation during previous yr — any vs. none	5.72 (4.47–7.31)	<0.001	2.24 (1.77–2.84)	<0.001	2.55 (1.96–3.31)	<0.001	<0.001
FEV_1 — per 100-ml decrease	1.11 (1.08–1.14)	<0.001	1.06 (1.03–1.08)	<0.001	1.05 (1.02–1.09)	<0.001	<0.001
SGRQ score for COPD — per increase of 4 points	1.07 (1.04–1.10)	<0.001	1.01 (0.99–1.04)	0.38	1.06 (1.03–1.09)	<0.001	<0.001
History of reflux or heartburn — yes vs. no	2.07 (1.58–2.72)	<0.001	1.61 (1.23–2.10)	<0.001	1.29 (0.97–1.70)	<0.005	<0.001
White-cell count — per increase of $1\times10^3/mm^3$	1.08 (1.03–1.14)	0.002	1.02 (0.97–1.08)	0.45	1.06 (1.01–1.12)	<0.001	0.007

* FEV_1 denotes forced expiratory volume in 1 second, and SGRQ St. George's Respiratory Questionnaire.

are shown in Table 3. Exacerbations were significantly associated with worsening lung function (according to post-bronchodilator FEV_1), greater impairment in health status (quality of life), a history of gastroesophageal reflux, and an increased white-cell count.

STABILITY OF THE FREQUENT-EXACERBATION PHENOTYPE

To assess the stability of the frequent-exacerbation phenotype over time, we first assessed how well patients' recall of treated exacerbations in the year before study entry predicted the number of exacerbations in year 1, calculating positive predictive values and negative predictive values. These analyses included data from the 1679 patients who completed all 3 years of the study.

Among the 1318 patients reporting no exacerbation or one exacerbation in the year before enrollment (infrequent exacerbations), 1037 also had infrequent exacerbations in the first year of the study (negative predictive value, 79%). Among the 361 patients reporting two or more exacerbations in the year before enrollment (frequent exacerbations), 211 also had frequent exacerbations in the first year of the study (positive predictive value, 58%); 289 of these patients (80%) had at least one exacerbation. Previous exacerbation frequency as recalled by patients therefore had a sensitivity of 43% and a specificity of 87% for actual exacerbation frequency in the following year.

We next examined the stability of exacerbation frequency between study years 1 and 2. Among the 1187 patients with infrequent exacerbations during year 1, a total of 987 had infrequent exacerbations in year 2 (negative predictive value, 83%). Among the 492 patients with frequent exacerbations in year 1, there were 296 who had frequent exacerbations in year 2 (positive predictive value, 60%); 84% of patients with frequent exacerbations in year 1 had at least one exacerbation in year 2. Thus, exacerbation frequency in the first year had a sensitivity of 60% and a specificity of 83% for the frequency in the second year.

Among the 1183 patients with infrequent exacerbations in year 2 of the study, 994 also had infrequent exacerbations in year 3 (negative predictive value, 84%). Among the 496 patients with frequent exacerbations in year 2, there were 276 who had frequent exacerbations in year 3 (positive predictive value, 56%).

Over the three-year study period, the phenotypes for exacerbation susceptibility and resistance became stronger. Among 296 patients who had frequent exacerbations in years 1 and 2, there were 210 (71%) who went on to have frequent exacerbations in year 3, and among 521 patients with no exacerbation in year 1 or year 2, a total of 388 (74%) also had no exacerbation in year 3. The stability of exacerbation frequency is shown in Figure 2.

EXACERBATION FREQUENCY ACCORDING TO DISEASE SEVERITY

Among the 945 patients with moderate COPD, 208 (22%) had frequent exacerbations (two or more during the first year of the study). (The characteristics of patients with moderate COPD are listed

according to exacerbation frequency in Table 1 in the Supplementary Appendix.) To further characterize patients with moderate COPD who had the frequent-exacerbation phenotype, we repeated the stepwise multinomial regression analysis, this time including only these patients. Because there was a high degree of confounding with sex in this model, associations were explored for each sex separately. The results are reported in Table 4. Exacerbations were significantly more common in women with moderate COPD than in men with moderate COPD: 1.02 versus 0.74 exacerbations per person per year (P<0.001). As in the full cohort, among both men and women, the variable most strongly associated with exacerbations during the first year of follow-up was a history of exacerbations. A greater impairment in health status (quality of life) was associated with exacerbations in the overall cohort of patients with moderate COPD, but the association was not observed in the models in which each sex was analyzed separately.

Among the 293 patients in the study who had very severe COPD, 138 (47%) had frequent exacerbations (two or more) during the first year of the study, and 84 (29%) had no exacerbations. (The characteristics of patients with very severe COPD, categorized according to exacerbation frequency, are listed in Table 2 in the Supplementary Appendix.) In a stepwise logistic-regression analysis, the patients with very severe COPD who did not have exacerbations during the 3-year study period were those who did not have exacerbations in the year before study entry (odds ratio, 4.53; 95% CI, 2.62 to 7.82; P<0.001). No other variables were significantly associated with exacerbations, and in this group of patients, there was no association between exacerbation frequency and health status (as assessed with the use of the St. George's Respiratory Questionnaire). (The characteristics of patients with severe COPD, categorized according to exacerbation frequency, are listed in Tables 3 and 4 in the Supplementary Appendix).

DISCUSSION

Using data from the large observational ECLIPSE cohort, we examined the frequency of exacerbations among patients with moderate, severe, or very severe COPD. We found that one group of patients appeared to be susceptible to exacerbations, irrespective of disease severity as defined by spirometric assessment of lung function. This phenotype of susceptibility to exacerbations could be identified by asking patients about previous exacerbations and was relatively stable over a 3-year period.

A range of variables have inconsistently been associated with exacerbation frequency in previous studies.[8-10] We have provided robust data from a single study showing that exacerbations requiring treatment become more frequent as the severity of COPD increases. Our study concerns moderate and severe exacerbations, which are the most burdensome to patients and health care services, among patients with a wide spectrum of COPD severity and in whom the underlying disease has been comprehensively assessed. Our conservative definition of exacerbation probably underestimates the frequency of symptom-defined events.[8] Nevertheless, the proportion of patients with GOLD stage 4 disease who had frequent exacerbations (two or more annually) was more than twice the proportion of patients with GOLD stage 2 disease who had frequent exacerbations. Our data also support the view that the consequences of exacerbation become more severe with increasing disease severity. However, differentiating the severity of exacerbations from the severity of the underlying disease is complex.

The major determinant of frequent exacerbations in all GOLD stages of COPD severity that we examined was a history of exacerbations. Our results suggest that COPD with frequent exacerbations is a distinct phenotype that is seen in moderate and severe stages of disease and that the incidence of frequent exacerbations increases with increasing disease severity. We use the term "distinct" in reference to a subgroup of patients who appear to be particularly susceptible to these events, accepting that exacerbation frequency is a continuous variable. There is currently much interest in defining specific phenotypes in COPD that may have different prognoses or treatment requirements.[19] Our data suggest that the frequent-exacerbation phenotype can be identified on the basis of a history of exacerbations, potentially allowing for appropriate targeting of patients for interventions and making it possible to selectively recruit patients for clinical trials. Status with respect to exacerbation frequency appears to be relatively stable over time, especially in the case of patients who do not have exacerbations. This suggests that the phenotype of frequent ex-

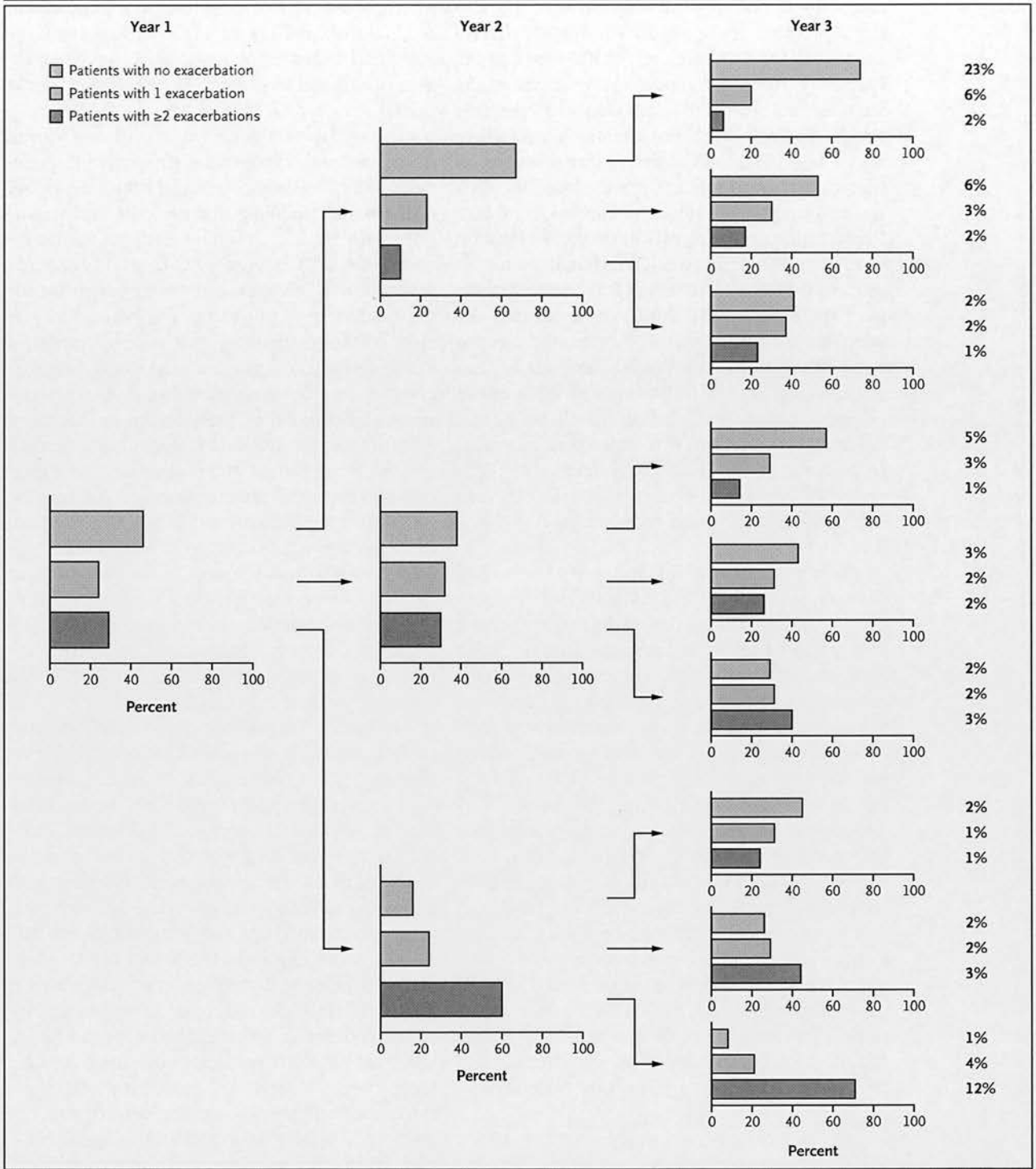

Figure 2. Stability of the Frequent-Exacerbation Phenotype in the 1679 Patients with Chronic Obstructive Pulmonary Disease Who Completed the Study.

The bars at the left show the proportions of patients with no exacerbations, one exacerbation, or two or more exacerbations in year 1. The bars in the middle show the respective incidence of exacerbations for these patients in year 2; the bars at the right show the respective incidence in year 3. The percentages at right denote the proportions of all patients with no exacerbations, one exacerbation, or two or more exacerbations. Numbers do not sum to 100 because of rounding.

Table 4. Factors Associated with Increased Exacerbation Frequency in Patients with Moderate (GOLD Stage 2) COPD, According to Sex.

Factor	Number of Exacerbations						Overall P Value
	≥2 vs. 0		1 vs. 0		≥2 vs. 1		
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*	*odds ratio (95% CI)*	*P value*	
Women (N=376)							
Exacerbation during previous year — yes vs. no	8.89 (4.32–18.29)	<0.001	2.28 (1.26–4.11)	<0.006	3.90 (1.82–8.34)	<0.001	<0.001
History of asthma — yes vs. no	3.38 (1.62–7.05)	<0.001	3.00 (1.59–5.66)	<0.001	1.12 (0.53–2.38)	0.76	<0.001
Fibrinogen — per increase of 1 SD on log scale	1.95 (1.28–2.97)	<0.002	1.22 (0.85–1.74)	0.28	1.60 (1.03–2.49)	<0.04	0.008
Men (N=569)							
Exacerbation during previous yr — yes vs. no	7.38 (4.44–12.27)	<0.001	3.28 (2.09–5.13)	<0.001	2.25 (1.30–3.90)	0.004	<0.001
FEV_1 — per 100-ml decrease*	1.20 (1.11–1.31)	<0.001	1.07 (1.00–1.14)	<0.05	1.13 (1.04–1.23)	<0.006	<0.001
Chronic wheezing — yes vs. no	2.56 (1.55–4.23)	<0.001	1.40 (0.89–2.18)	0.14	1.83 (1.06–3.16)	<0.03	0.001

* FEV_1 denotes forced expiratory volume in 1 second, and NS not significant.

acerbations may best be described as an exacerbation-susceptibility phenotype, in which persons with the phenotype are prone to exacerbations as a result of intrinsic susceptibility and have exacerbations on exposure to particular triggers, such as respiratory viral infection.[20]

In the multivariate analysis of data for the entire cohort, in addition to the association with previous exacerbations and with greater disease severity, more frequent exacerbations were associated with greater impairment in health status, a history of gastroesophageal reflux, and an elevated white-cell count. Sex was associated with exacerbation frequency, but it was confounded with other variables. It has previously been reported that patients with frequent exacerbations may have increased airway inflammation in the stable state.[21] The relationship that we observed between exacerbation frequency and health status has been noted previously,[4] as has the association of exacerbations with gastroesophageal reflux.[22] In contrast, chronic bronchitis was not associated with exacerbations in any of our analyses, despite previous reports that cough and sputum production are related to exacerbations in COPD.[23-25]

Among the patients who had moderate COPD, 22% had frequent exacerbations — an important observation, considering that such patients, who have relatively mild disease according to FEV_1 criteria, may not at present be identified for interventions to reduce exacerbations. Since moderate COPD is more prevalent than very severe COPD,[26] the overall burden of exacerbations may be greater with milder disease. In the group of patients with moderate disease in our study, exacerbations were more common among women than among men, and there were other factors that varied according to sex. The observation of sex-based differences in exacerbation frequency is intriguing, and it is not clear whether the higher rate of exacerbations among women represents a real increase in exacerbations, women's heightened awareness of symptoms, or a greater tendency on the part of women to report such changes in symptoms to a health care provider. Regarding features that could suggest airway hyperreactivity, such as wheezing or a history of asthma, bronchodilator reversibility criteria were not used as criteria for inclusion or exclusion in the ECLIPSE study. The question of whether clinically significant airway hyperresponsiveness is also a distinct phenotype in COPD requires further study.

Among the patients in the study who had very severe COPD, 29% appeared to have had resistance to exacerbations, although some of these patients may have been unable to recognize an

exacerbation (which may therefore not have been reported to their physician for treatment).[4,27] This finding also has potential implications for therapy, in that it may not be necessary to take aggressive approaches to the prevention of exacerbations in patients with very severe COPD if they do not have a history of such events. In our study, patients with very severe disease who did not have exacerbations did not have any other characteristics distinguishing them from patients with exacerbations except for the fact that they did not report exacerbations in the preceding year.

Although exacerbation frequency was associated with health status across the GOLD stages and in patients with moderate (stage 2) disease, this was not true among patients with the most severe disease (stage 4). Whether this trend reflects the smaller number of patients with very severe disease or a survivor effect among patients with severe disease who were participating in a longitudinal study cannot be established. Another possibility is that in patients with very severe COPD, the role of exacerbations in compromising health status is less important than that of the severity of the underlying disease itself.

The main strength of this analysis is the use of a large cohort of patients with COPD and a range of disease severity. Some important negative findings deserve mention — in particular, the fact that we did not find an association between smoking status and exacerbation frequency.[4] However, our cohort was not a population sample but a sample of symptomatic patients known to respiratory physicians. Controlled trials have shown that pharmacotherapy can reduce exacerbations.[9,10] We did not focus on medication as a determinant of exacerbations. Evidence-based treatment of COPD often includes the use of a history of exacerbation as an indicator for starting treatment[12]; in an observational study, exacerbations are therefore likely to predict treatment — not vice versa.

In conclusion, our study confirms the observation that exacerbations become more frequent and more severe as the severity of underlying COPD increases and shows that the most important determinant of frequent exacerbations is a history of exacerbations. This finding supports the hypothesis that patients who are more subject to frequent exacerbations, some of whom have milder disease, have a distinct susceptibility phenotype that is relatively stable over time and can be identified on the basis of the patient's recall of previously treated events.

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APPENDIX

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Lung Mechanics and Dyspnea during Exacerbations of Chronic Obstructive Pulmonary Disease

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Rationale: **Exacerbation of chronic obstructive pulmonary disease commonly causes hospitalization. The change in lung mechanics during exacerbation and its relationship to symptoms in spontaneously breathing individuals has not been described.**

Objective: **We hypothesized that changes in both airflow and lung volumes would occur during an exacerbation, but that only volume change would relate to symptomatic improvement.**

Methods: **Lung mechanics and resting dyspnea were recorded in 22 hospitalized patients during recovery from exacerbation.**

Measurements: **Spirometry, inspiratory capacity, respiratory system resistance and reactance, tidal breathing patterns, and expiratory flow limitation were recorded after nebulized bronchodilator therapy on the first 3 d after admission, at discharge, and 6 wk postadmission (Day 42). Prebronchodilator measurements were taken on Day 2, at discharge, and on Day 42.**

Main Results: **Postbronchodilator inspiratory capacity increased 0.23 ± 0.07 L by discharge and 0.42 ± 0.1 L by Day 42, FEV_1 rose 0.09 ± 0.04 and 0.2 ± 0.05 L at discharge and Day 42, respectively, and FVC increased 0.21 ± 0.08 and 0.47 ± 0.09 L at discharge and Day 42 (all $p < 0.05$). Consistent reduction in dyspnea was seen as the exacerbation resolved. Respiratory system resistance, FEV_1/FVC, and expiratory flow limitation were unchanged throughout, indicating that changes in lung volume rather than airflow resistance predominated.**

Conclusions: **Improvement in operating lung volumes is the principal change seen as a chronic obstructive pulmonary disease exacerbation resolves and increase in inspiratory capacity is a useful guide to a reduction in dyspnea.**

Keywords: breathlessness; inspiratory reserve volume; lung function; lung hyperinflation

Periodic exacerbations of symptoms are a major cause of morbidity, mortality, and health care costs in patients with chronic obstructive pulmonary disease (COPD) (1, 2). They are associated with a worse quality of life (3, 4) and a more rapid decline in both health status (4) and FEV_1 (5, 6). Most exacerbations are precipitated by either bacterial or viral infections (7, 8), but the resulting symptoms relate mainly to altered lung function. Increased cough, sputum production, and sputum purulence occur during exacerbations, but patients identify the most important symptom as being worsening breathlessness (9, 10). Although changes in lung mechanics are thought to be the major cause of dyspnea in COPD, we have few data about the time course and nature of the change in lung mechanics during the resolution of an exacerbation in normocapnic patients.

Studies of patients in intensive care units have shown that the resistive and elastic work of breathing increases significantly during exacerbations, which leads to a marked increase in intrinsic positive end-expiratory pressure (11, 12). How these changes relate to more familiar measurements of flow and volume or to changes in symptom intensity in spontaneously breathing subjects has not been reported, but several mechanisms appear possible. Increased airway resistance, due to the release of mediators or the direct effect of inflammation reducing airway diameter, should lessen as the exacerbation resolves and be reflected by an increase in peak expiratory flow or FEV_1. However, the changes reported in these measures during an exacerbation of COPD are relatively small (13). Tidal expiratory flow limitation (EFL) is a better indicator of dyspnea severity than is the FEV_1 in stable COPD (14), and thus changes in EFL due to airway narrowing or closure during an exacerbation of COPD might relate to changes in symptom intensity. The relationship of EFL to other indices of lung mechanics during exacerbations has not been reported. However, the factor most likely to explain the change in symptoms during an exacerbation is a change in operating lung volume. An increase in end-expiratory lung volume (EELV) during exercise is the best predictor of symptom intensity and the degree of exercise limitation (15), and both improve after administration of a bronchodilator drug (16). During an exacerbation of COPD closure of small airways may occur because of mucus plugging, airway wall edema, or inflammation of lymph follicles, all of which may increase EELV even under resting conditions (17).

We hypothesized that during the resolution of an exacerbation of COPD there would be larger changes in lung volume than in expiratory flow–related measurements. It proved impractical to study the onset of an exacerbation and thus we prospectively studied patients on admission to hospital and monitored their subsequent clinical course. To compare patients we standardized treatment given and measurement timing as well as prior bronchodilator therapy. We recorded pre- and postbronchodilator values for spirometry, dynamic lung volumes, oscillatory lung mechanics, and breathing pattern and tested for the presence of tidal expiratory flow limitation, relating these to changes in dyspnea and clinical improvement. Some of the results of these studies have previously been reported in the form of abstracts (18–20).

METHODS

Subject Recruitment

Patients were recruited within 24 h of hospitalization. An acute exacerbation was defined as an increase in at least two major symptoms: dyspnea, sputum purulence, or increased sputum volume, sufficient to require hospitalization (21). Patients were excluded if they had acute pneumonia, pneumothorax, atelectasis, or heart failure; had respiratory acidosis ($pH < 7.32$); had a coexisting illness that rendered them too ill to participate; or were unwilling to participate. All patients had a diagnosis of COPD defined both clinically and physiologically (22) with

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an FEV_1 less than 80% predicted and an FEV_1/FVC ratio less than 0.7 when enrolled (23). Any patient in whom the FEV_1 increased by more than 400 ml after administration of nebulized bronchodilator (24) or whose lung function improved to within normal values at any test session was excluded. Written informed consent was obtained from each patient. The local research ethics committee granted study approval (*see* the online supplement for further details).

Inpatient Management of Exacerbation

All patients were managed by a respiratory physician who determined the time of discharge on clinical grounds without knowledge of the study measurements. While hospitalized, patients received regular nebulized salbutamol and ipratropium bromide (5 mg and 0.5 mg per nebulization, respectively) and oral corticosteroids (30 mg daily for 1 wk), and most patients received antibiotics (usually a broad-spectrum penicillin) as directed by their clinician.

Study Design

Postbronchodilator assessments were made daily for the first 3 d (Days 1, 2, and 3), at discharge and, when possible, on Day 42 (6 wk postadmission). Additional prebronchodilator data were obtained on Day 2, at discharge, and, when possible, on Day 42. All prebronchodilator tests were performed in the morning with no bronchodilator therapy for 6 h beforehand. Patients subsequently received nebulized salbutamol (5 mg) and ipratropium bromide (0.5 mg). Forty-five minutes later, the tests were repeated. Tests were performed in the same sequence at each visit and comprised measurement of flow limitation, resting tidal breathing analysis, measurement of respiratory system resistance and reactance during tidal breathing, inspiratory capacity (IC), and spirometry (*see* the online supplement for further details).

Measurements

Spirometry and IC. Spirometry was measured to American Thoracic Society standards (23), using a pneumotachograph (Jaeger MasterScreen IOS; VIASYS Healthcare, Hoechberg, Germany). IC was calculated indirectly by measuring the expiratory reserve volume (ERV) and VC, also using the same pneumotachograph. Testing was repeated until two reproducible values within 10% of each other were obtained; the best being recorded. Predicted IC was derived from combined total lung capacity (TLC) and FRC predictions. Inspiratory reserve volume (IRV) was calculated by subtracting V_T from IC.

Measurement of total respiratory system resistance and reactance. Respiratory system resistance at a frequency of 5 Hz (R_5) and reactance at 5 Hz (X_5) was measured by impulse oscillometry (Jaeger MasterScreen IOS); the apparatus deadspace was 120 ml. At least five tidal breaths of the same duration and volume were recorded and the analyzed data were averaged over this time period. Measurements were repeated until two values that were within 10% of each other were obtained. The mean value of these measurements was used for analysis (25).

Tidal breathing and resting expiratory flow limitation. Resting breathing was recorded with the pneumotachograph system for 3 min, with data analyzed during the final minute. Respiratory rate, V_T, inspiratory and expiratory times and their derivatives, mean inspiratory and expiratory flow (V_T/inspiratory time [T_I] and V_T/expiratory time [T_E], respectively), duty cycle (T_I/total cycle duration [Ttot]), and $\dot{V}_E$ were calculated.

Negative expiratory pressure during tidal breathing was applied to detect expiratory flow limitation in the seated patient, as described previously (26). Breaths were considered flow limited when negative expiratory pressure did not increase expiratory flow relative to the preceding untested breath. Flow limitation was also expressed as the percentage of expired tidal volume affected (FL % V_T).

Assessment of Dyspnea

Before each testing sequence patients were asked to rate the intensity of their resting breathlessness on a modified Borg scale, in response to the question: "How breathless do you feel?" (27).

See the online supplement for additional detail on the methods used to make all these measurements.

Statistical Analysis

Data are expressed as means (SD) for group data or as means ± SEM when time points or groups are compared. We used a Student *t* test and repeated measures analysis of variance to compare differences in normally distributed data (SPSS version 10.0; SPSS, Chicago, IL), accepting $p < 0.05$ as significant. On the basis of the known test–test reproducibility of inspiratory capacity (26), we needed 14 patients to detect a 200-ml difference in IC from entry to study conclusion. We anticipated that we might have a 35% dropout with this protocol and planned to recruit at least 21 individuals.

RESULTS

Clinical Characteristics of the Study Population

Of 44 patients identified as being potentially eligible over an 18-mo period, 30 entered the study but 7 withdrew during the early stages because of clinical deterioration (n = 5) or technical difficulty in completing maneuvers (n = 2). One patient was excluded as that patient's lung function subsequently returned to normal. The admission characteristics of the remaining 22 patients are shown in Table 1.

All patients reported symptoms consistent with an acute exacerbation before admission to hospital. Four patients had received antibiotics and/or oral corticosteroids in the week before admission. No patient had been admitted with an exacerbation of COPD in the preceding 6 wk. Three patients received intravenous aminophylline and none required ventilation or died. The median length of hospital stay was 7 d (range, 3–10 d). Two patients were discharged on Day 3 and their measurements on Day 3 were also included in the discharge day data. *See* the online supplement for sputum microbiological data. Neither the presence of microorganisms in the sputum nor the treatment received before admission appeared to influence the changes in lung mechanics seen during recovery from the exacerbation.

Data for 6 of the 22 patients were not available for Day 42, either because of recurrent exacerbations of COPD (n = 5) or because the patient declined to attend for these follow-up studies (n = 1). Admission data for the 16 patients who returned on Day 42 are shown in Table 1. Admission characteristics of the subjects who returned on Day 42 did not differ from those who did not (Table 1), nor did the data at discharge (data not presented).

Changes in Lung Mechanics during the Exacerbation

Postbronchodilator spirometry and lung volume. Changes in postbronchodilator spirometry and IC from admission to discharge and, when available, to Day 42 for all subjects are shown in Figure 1 and Table 2. Group mean postbronchodilator FEV_1 improved by 0.09 ± 0.04 L at discharge ($n = 22$, $p < 0.05$) and by 0.20 ± 0.05 L ($n = 16$, $p < 0.01$) by Day 42 relative to the Day 1 value. Postbronchodilator FVC improved by 0.2 ± 0.08 L ($n = 22$, $p < 0.05$) on discharge and by Day 42 had increased 0.47 ± 0.09 L from the admission value ($n = 16$, $p < 0.001$). There was no change in FEV_1/FVC ratio at any stage; for example, the ratio was 0.49 on admission and 0.48 on Day 42 (p = not significant). These data were not different if slow vital capacity data were substituted for the FVC.

IC increased from Day 1, when it was 62 ± 4% predicted at admission, to 73 ± 4% at discharge ($n = 22$, $p < 0.05$), and to 81 ± 7% on Day 42 ($n = 16$, $p < 0.01$). These values correspond to an improvement of 0.23 ± 0.07 L ($p < 0.01$) by discharge and 0.42 ± 0.1 L ($p < 0.01$) by Day 42; *see also* Table 2. The change in IC from admission to discharge was related to the change in FVC ($r = 0.47$, $p < 0.05$) but not the change in FEV_1.

Respiratory system resistance and reactance. There was no significant change in respiratory system resistance, R_5, throughout the study. Thus the R_5 fell from 0.65 ± 0.04 to 0.59 ± 0.04 kPa/L/s on discharge, whereas in those in whom it was recorded on Day 42 the R_5 was 0.61 ± 0.2 on admission and 0.58 ± 0.04 on Day 42 (Tables 1 and 2 and Figure 2A).

TABLE 1. ADMISSION CHARACTERISTICS OF ALL SUBJECTS WHO WERE MONITORED TO DISCHARGE AND OF THE 16 SUBJECTS WHO COMPLETED 42 DAYS OF FOLLOW-UP

	All Subjects	Subjects Attending on Day 42
No. subjects (no. males)	22 (9)	16 (7)
Age, yr	70 (10.3)	69 (9.9)
Smoking, pack-yr	47 (22.5)	45 (15.5)
Body mass index, kg/m²	21.9 (4.8)	22.3 (4.8)
White cell count, × 10⁹/L	11.50 (4.36)	11.42 (4.83)
Borg breathlessness score at rest on first assessment	3.7 (1.6)	3.9 (1.8)
pH	7.41 (0.05)	7.40 (0.05)
Pa_{O_2}, kPa	8.97 (1.40)	8.94 (1.51)
Pa_{CO_2}, kPa	5.02 (0.88)	5.04 (0.99)
FEV_1, L	1.03 (0.36)	1.06 (0.40)
FEV_1, %pred	46.7 (18.1)	46.8 (19.2)
FVC, L	2.15 (0.57)	2.08 (0.51)
IC, L	1.37 (0.43)	1.32 (0.39)
IC, %pred	62.2 (16.3)	59.3 (16.4)
Total respiratory system resistance		
R_5, kPa/L/s	0.65 (0.2)	0.61 (0.2)
X_5, kPa/L/s	−0.42 (0.16)	−0.40 (0.19)
No. subjects with resting EFL	9	7

Definition of abbreviations: EFL = tidal expiratory flow limitation assessed by negative expiratory pressure technique; IC = inspiratory capacity; R_5 = total respiratory system resistance; X_5 = total respiratory system reactance.

Values represent means (SD). No statistically significant differences were seen between the groups.

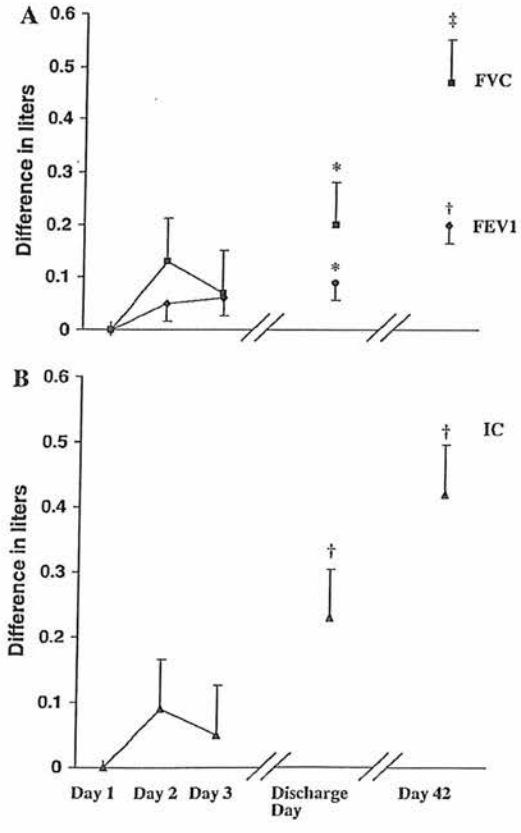

Figure 1. (*A*) Difference in FEV_1 and FVC over time from day of admission (Day 1) to discharge (median, Day 7) and postdischarge (Day 42). (*B*) Difference in inspiratory capacity (IC) over time from day of admission (Day 1) to discharge (median, Day 7) and postdischarge (Day 42). *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$, discharge and Day 42 compared with Day 1. Note that data for Day 42 apply to 16 patients only (*see* Tables 1 and 2 for relevant baseline and Day 42 data).

The group mean respiratory system reactance measured at 5 Hz, X_5, improved from admission to discharge by 0.11 ± 0.02 kPa/L/s ($p < 0.001$) and was not significantly different on Day 42 (Table 2 and Figure 2B). From admission to discharge postbronchodilator X_5 became less negative in 16 subjects (–0.45 ± 0.04 to –0.29 ± 0.04 kPa/L/s) and remained constant in the other 6 patients. There were no significant differences on admission between patients whose X_5 improved over time and those for whom it did not. The "X_5 improvers" had significant improvements in FEV_1 (mean change, 130 ml; $p < 0.05$) and IC (mean change, 270 ml; $p < 0.01$) whereas the "nonimprovers" did not show significant improvement (*see* Table E1 in the online supplement).

Breathing pattern. The postbronchodilator breathing pattern at rest did not change significantly during the recovery period (Table 3). Resting $\dot{V}E$ remained relatively high at each test session despite the improvement in other measurements of lung mechanics. A significant increase in IRV of 0.2 ± 0.1 L ($p < 0.05$) occurred during the in-hospital period. There was a further change in outpatient recovery period: on Day 42, IRV increasing from admission by 0.27 ± 0.64 L ($n = 16$, $p = 0.05$).

Tidal flow limitation during exacerbation. On admission, when seated, 9 of the 22 patients showed EFL, whereas 13 were not tidal flow limited. EFL resolved in four patients and appeared for the first time by discharge in two patients; the remaining 16 patients were unchanged. In EFL, subjects' mean percentage of FL as a percentage of VT (FL % VT) was 44 ± 3% at baseline. There was no clear pattern of change or improvement in FL % VT during recovery.

Bronchodilator Response during Exacerbation

Changes in lung mechanics, breathing pattern, and dyspnea after nebulized bronchodilators are presented in Table 4. There was a significant increase in FEV_1, FVC, IC, and X_5 after bronchodilator administration, accompanied by a fall in dyspnea score and R_5. The increase in FEV_1 ($p < 0.04$) and fall in R_5 ($p < 0.01$) immediately after bronchodilator administration was greater as the exacerbation resolved. The improvement in IC, FVC, and Borg score was similar irrespective of the time after admission that the test was performed.

Breathing pattern was little affected by the bronchodilator, with a small but significant increase in VT occurring on Day 2

TABLE 2. CHANGE IN LUNG MECHANICS AND SYMPTOMS OVER THE COURSE OF THE FIRST 3 DAYS OF HOSPITALIZATION, AT THE TIME OF DISCHARGE, AND ON DAY 42

	Day 1	Day 2	Day 3	Discharge Day	Day 42
No. subjects	22	22	22	22	16
FEV_1, L	1.03 ± 0.08	1.08 ± 0.08*	1.08 ± 0.08	1.12 ± 0.09*	1.26 ± 0.10†
FEV_1, %pred	47.0 ± 3.9	49.2 ± 4.1*	49.4 ± 4.2	51.2 ± 4.6*	54.8 ± 4.2*
FVC, L	2.15 ± 0.12	2.28 ± 0.2	2.23 ± 0.14	2.36 ± 0.12*	2.54 ± 0.14‡
FVC, %pred	76.9 ± 4.8	80.2 ± 4.4	78.0 ± 4.3	83.5 ± 4.1*	86.3 ± 3.1†
FEV_1/FVC	0.49 ± 0.03	0.48 ± 0.03	0.50 ± 0.03	0.48 ± 0.03	0.49 ± 0.03
IC, L	1.37 ± 0.1	1.46 ± 0.1	1.43 ± 0.10	1.60 ± 0.10†	1.74 ± 0.13†
Borg score	3.73 ± 0.34	3.03 ± 0.34*	3.07 ± 0.30†	2.47 ± 0.24†	2.16 ± 0.30†
R_5, kPa/L/s	0.65 ± 0.04	0.60 ± 0.04	0.65 ± 0.04	0.59 ± 0.04	0.58 ± 0.04
X_5, kPa/L/s	−0.42 ± 0.03	−0.37 ± 0.04	−0.39 ± 0.04	−0.31 ± 0.03‡	−0.28 ± 0.04†

Definition of abbreviations: IC = inspiratory capacity; R_5 = total respiratory system resistance; X_5 = total respiratory system reactance. Values represent means ± SEM.

* $p < 0.05$, significant difference compared with Day 1.

† $p < 0.01$, significant difference compared with Day 1.

‡ $p < 0.001$, significant difference compared with Day 1.

(+80 ml) and Day 42 (+70 ml). Expressing the IC as a percentage of the FVC showed no acute change with bronchodilator administration, although the postbronchodilator IC/FVC ratio value rose from 64% on Day 2 to 68% at discharge. The acute change in IRV was small on Day 2 but increased by a mean of 120 ml ($p < 0.05$) on discharge and by 240 ml ($p < 0.05$) on Day 42.

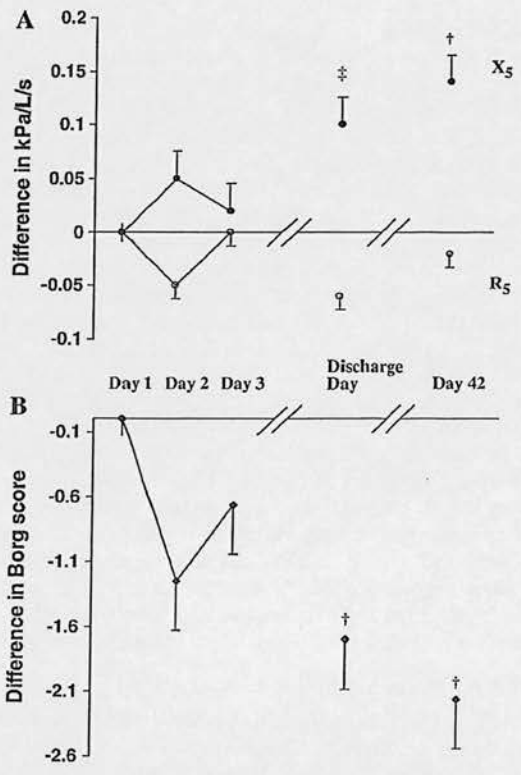

Figure 2. (*A*) Difference in total respiratory system resistance (R_5) and total respiratory system reactance (X_5) over time from day of admission (Day 1) to discharge (median, Day 7) and postdischarge (Day 42). (*B*) Difference in Borg breathlessness scores over time from day of admission (Day 1) to discharge (median, Day 7) and postdischarge (Day 42). †$p < 0.01$; ‡$p < 0.001$, discharge and Day 42 compared with Day 1. Note that data for Day 42 apply to 16 patients only (*see* Tables 1 and 2 for relevant baseline and Day 42 data).

Relative Change in Resting Breathlessness and Lung Mechanics

The median resting postbronchodilator Borg breathlessness score on admission was 4 (range, 0.5–7). There was a fall in postbronchodilator breathlessness score, relative to Day 1, of 1.7 ± 0.43 units at discharge ($p < 0.01$) and 2.16 ± 0.4 units on Day 42 ($p < 0.01$) with median scores of 2.5 (range, 0–4) and 2 (range, 0–5), respectively (Figure 2B).

Only 16 of 22 patients reported any reduction in resting dyspnea by discharge. These patients had a significantly lower IC on admission compared with patients not reporting a reduction in dyspnea ($p < 0.01$). Both FEV_1 and IRV were also lower in this group on admission (both $p = 0.05$). The degree of resting dyspnea these patients reported on discharge was similar to that on admission among the patients whose dyspnea did not improve over time (*see* Table E2).

In patients whose Borg score improved during hospitalization, mean FEV_1 increased by 0.20 ± 0.07 L ($p < 0.05$), mean IC by 0.54 ± 0.16 L ($p < 0.01$), and mean X_5 by 0.15 ± 0.04 kPa/L/s ($p < 0.01$) by Day 42 ($n = 11$). In contrast, in those whose dyspnea was unchanged, neither FEV_1 nor IC increased significantly (*see* Table E2). Similar changes were seen in each of these variables at the time of discharge although these were generally of a smaller magnitude. By discharge, there was no significant difference in IC between patients who felt an improvement in breathlessness and those who did not. The magnitude of the change in dyspnea from admission to discharge or follow-up was unrelated to the change in IC or other measured variables.

DISCUSSION

Although exacerbations of COPD are a frequent cause of hospitalization, surprisingly little is known about the physiologic changes that accompany their resolution and what relationship these bear to the patient's symptoms. Hypoxia and hypercapnia have been carefully studied, with the latter relating directly to lung mechanics (28) and showing a variable resolution over time (29) and between episodes (30). Our data demonstrate that from admission to discharge and through the 6 wk after the exacerbation there was a small increase in FEV_1, no significant change in airway resistance or tidal FL, but a significant increase in both FVC and IC together with an improvement in reactance. In nonhypercapnic exacerbations, changes in operating lung volumes rather than either tidal or forced expiratory flow related to both the resolution of the exacerbation and the change in breathlessness reported by the patient.

TABLE 3. BREATHING PATTERN DATA FOR ALL 22 SUBJECTS DURING THE FIRST 3 DAYS OF HOSPITALIZATION, ON THE DAY OF DISCHARGE, AND ON DAY 42

	Day 1	Day 2	Day 3	Discharge Day	Day 42
No. subjects	22	22	22	22	16
V_T, L	0.75 ± 0.05	0.76 ± 0.04	0.75 ± 0.04	0.78 ± 0.04	0.83 ± 0.06*
F, min^{-1}	22.15 ± 0.9	23.05 ± 1.2	22.78 ± 1.4	21.93 ± 1.0	21.6 ± 0.9
$\dot{V}_E$, L · min^{-1}	16.8 ± 1.5	17.1 ± 0.8	16.71 ± 0.9	16.73 ± 0.9	16.1 ± 1.5
T_I, s	1.02 ± 0.05	0.99 ± 0.05	1.04 ± 0.07	1.05 ± 0.04	1.12 ± 0.04
T_E, s	1.77 ± 0.07	1.74 ± 0.08	1.83 ± 0.14	1.79 ± 0.09	1.75 ± 0.08
V_T/T_I	0.77 ± 0.06	0.80 ± 0.04	0.77 ± 0.04	0.75 ± 0.04	0.69 ± 0.06
V_T/T_E	0.45 ± 0.04	0.45 ± 0.02	0.44 ± 0.02	0.45 ± 0.03	0.45 ± 0.04
V_T/IC	0.57 ± 0.04	0.55 ± 0.03	0.59 ± 0.05	0.52 ± 0.03	0.49 ± 0.05
IRV, L	0.62 ± 0.08	0.71 ± 0.09	0.67 ± 0.08	0.82 ± 0.1*	0.97 ± 0.16*

Definition of abbreviations: F = breath frequency; IRV = inspiratory reserve volume; T_E = expiratory time; T_I = inspiratory time; V_T/T_E = mean expiratory flow; V_T/T_I = mean inspiratory flow; V_T/IC = ratio of V_T to IC.

Values represent means ± SEM. Statistically significant differences compared with Day 1 are shown.

* $p < 0.05$, significant difference compared with Day 1.

A particular strength of this study is the assessment of both flow- and volume-related measurements at standardized times and with standardized therapy as the exacerbation resolved. Treatment before or during admission, including theophylline use, did not influence lung mechanics, in keeping with another report (31). All measurements were made at rest and so we cannot assess the effect of dynamic changes in lung volume that are likely to occur on exercise in these patients (32). We did not measure TLC by body plethysmography as this was not possible in these sick patients. Nonetheless, we believe it unlikely that TLC increased during recovery and instead either remained constant or fell. Hence we believe it likely that the change in postbronchodilator FVC and IC reflects a fall in residual volume over time. Likewise, the calculated $\dot{V}_E$ was higher in our patients than in other studies, which may reflect disease severity of the patients we studied or the arduous nature of the protocol. However, $\dot{V}_E$ was unchanged with time and is unlikely to influence the other indices of lung mechanics.

Noninvasive measurements of total respiratory system resistance and reactance were easy to make, were well tolerated, and provided information complementary to that obtained from the change in lung volumes. The accuracy of these data may be influenced in COPD by the presence of upper airway shunt compliance (33). This factor does not change acutely, and our data reported relative to the admission values are likely to be valid. We have reported data only at 5 Hz as this best reflects total respiratory system resistance rather than considering frequency dependence of resistance, a field in which the interpretation of oscillatory mechanics in COPD remains controversial. Tidal EFL was determined by the negative expiratory pressure technique in seated subjects. More information might have been obtained had the subjects been able to lie supine (34), although analysis of the percentage of each breath showing FL, a potentially more sensitive descriptor, did not change our results.

The small increase we observed in postbronchodilator FEV_1 from admission to discharge is similar to that reported previously (35). The changes in spirometry were due to an increase in volume rather than flow as judged by the static FEV_1/FVC ratio throughout the recovery period. This suggests that as the exacerbation resolved there was an opening of lung units with mechanical

TABLE 4. EFFECTS OF NEBULIZED BRONCHODILATORS ON LUNG MECHANICS, SYMPTOMS, AND BREATHING PATTERN DURING RECOVERY FROM EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	Day 2		Discharge		Day 42	
	Pre	Post	Pre	Post	Pre	Post
FEV_1, L	0.99 ± 0.07	1.08 ± 0.08	0.98 ± 0.09	1.12 ± 0.10*	1.04 ± 0.10	1.26 ± 0.11*
FVC, L	2.04 ± 0.14	2.28 ± 0.15*	2.05 ± 0.12	2.36 ± 0.13*	2.18 ± 0.13	2.55 ± 0.15*
IC, L	1.34 ± 0.13	1.46 ± 0.11	1.44 ± 0.12	1.60 ± 0.11*	1.49 ± 0.10	1.74 ± 0.13†
IRV, L	0.65 ± 0.11	0.71 ± 0.09	0.70 ± 0.10	0.82 ± 0.10†	0.73 ± 0.09	0.97 ± 0.14†
Borg score	3.6 ± 0.4	3.0 ± 0.4†	2.8 ± 0.2	2.5 ± 0.25†	2.8 ± 0.3	2.15 ± 0.3*
R_5, kPa/L/s	0.71 ± 0.04	0.60 ± 0.04*	0.77 ± 0.06	0.59 ± 0.05*	0.79 ± 0.05	0.58 ± 0.05*
X_5, kPa/L/s	−0.45 ± 0.04	−0.37 ± 0.04†	−0.50 ± 0.05	−0.31 ± 0.03*	−0.51 ± 0.05	−0.28 ± 0.04*
V_T, L	0.68 ± 0.16	0.76 ± 0.16‡	0.74 ± 0.19	0.77 ± 0.21	0.72 ± 0.18	0.79 ± 0.24†
F, min^{-1}	23.8 ± 5.8	23.0 ± 5.4	22.0 ± 5.2	22.6 ± 4.8	24.5 ± 6.1	22.0 ± 3.8†
T_I, s	0.97 ± 0.25	0.99 ± 0.24	1.07 ± 0.26	1.03 ± 0.20	0.99 ± 0.28	1.10 ± 0.21‡
T_E, s	1.67 ± 0.36	1.74 ± 0.39	1.82 ± 0.51	1.73 ± 0.40	1.60 ± 0.37	1.71 ± 0.35
$\dot{V}_E$, L · min^{-1}	16.2 ± 1.1	17.2 ± 0.8	16.3 ± 1.3	16.7 ± 0.9	16.9 ± 0.7	16.1 ± 1.3
V_T/T_I	0.75 ± 0.06	0.80 ± 0.04	0.72 ± 0.06	0.77 ± 0.04	0.74 ± 0.03	0.69 ± 0.06
V_T/T_E	0.43 ± 0.03	0.45 ± 0.02	0.43 ± 0.04	0.44 ± 0.03	0.46 ± 0.02	0.45 ± 0.04

Definition of abbreviations: F = breath frequency; IC = inspiratory capacity; IRV = inspiratory reserve volume; R_5 = total respiratory system resistance; T_I = inspiratory time; T_E = expiratory time; V_T/IC = ratio of V_T to IC; V_T/T_E = mean expiratory flow; V_T/T_I = mean inspiratory flow; X_5 = total respiratory system reactance.

Values represent means ± SEM. Analysis using paired Student *t* test comparing pre- and post-bronchodilator values.

* $p < 0.001$, significant difference in comparing pre and post results for each day.

† $p < 0.05$, significant difference in comparing pre and post results for each day.

‡ $p < 0.01$, significant difference in comparing pre and post results for each day.

properties similar to the lung at admission, as the unchanged FEV_1/FVC ratio reflects the mechanical time constant of the respiratory system. The IC increase in proportion to the FVC during the course of the exacerbation is in keeping with this, as is the relatively constant R_5 despite the fall in EELV. Respiratory frequency was also constant across the study days and did not seem to be an important determinant of the volume change at rest.

In our patients, we saw no consistent relationship between the presence of tidal EFL and the change in either IC or FVC over time. This might be due to breath-to-breath variation in the operating lung volume, as has been reported after administration of nebulized bronchodilators in stable COPD (26), but is more likely to reflect the change in residual volume over time. This contribution from a reduced static lung volume helps explain why the improvement in postbronchodilator inspiratory reserve volume occurred without any change in breathing pattern or respiratory timing.

Total respiratory system reactance became significantly less negative during recovery. This may in part result from the lower operating lung volume, but the magnitude of this change is larger than would be expected if this were the only operative factor. Taken together with the change in EELV and constant R_5, the data suggest that the "specific conductance" of the respiratory system was increasing as the patient improved but that individuals opt to reduce operating lung volume rather than to maintain a higher EELV with lower respiratory system resistance.

This is the first study of the response of patients with COPD to nebulized bronchodilators during and after an exacerbation. The large doses used are on the flat part of the dose–response curve for spirometry (36) and significantly improved FVC and Borg score at all time points support a relationship between operating lung volumes and breathlessness. In contrast, significant changes in FEV_1, IC, and reactance became apparent only on discharge, becoming larger in those monitored to 6 wk postadmission. These help explain why spirometric reversibility testing is unreliable soon after an exacerbation and why tests looking at FEV_1 change do not relate well to symptomatic response (37).

Increased breathlessness at rest is a common but not invariable accompaniment of COPD exacerbations (13). As in studies during exercise, Borg dyspnea scores were not normally distributed, but for comparison with other data in the literature we have reported them parametrically (15, 38, 39). Although these data can be indicative only of the direction of change, not its magnitude, we found that those patients reporting less breathlessness at the time of discharge and follow-up were the ones in whom IC and IRV improved significantly over this time, a change not seen in the smaller number of subjects in whom dyspnea remained constant. Patients reporting worse breathlessness at admission had significantly worse resting lung mechanics and larger studies will be needed to properly test the relationship between symptom change during exacerbation resolution and different measures of lung volume. Mechanically, the situation at rest during an exacerbation was comparable to that at maximal tolerated exercise when clinically stable, the change in postbronchodilator inspiratory capacity of 420 ml from Day 1 to Day 42 being comparable to the volume change reported during exercise (32, 40).

In summary, in normocapnic patients hospitalized with an exacerbation of COPD, improvement in operating lung volumes was related to reduction in dyspnea rather than any index of expiratory flow; however, it was measured. The impairment in resting lung mechanics resolved slowly and was not complete at the time of discharge as determined on the basis of clinical criteria. The relationship of resting lung mechanics on discharge to the dynamically regulated lung volume that usually determines exercise performance will require further study, as it may explain the variability in the subsequent clinical course postexacerbation.

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Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD

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► Additional tables and details of local protocols and of the six cases where COPD was diagnosed clinically are published online only at http://thorax.bmj.com/content/vol64/issue10

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ABSTRACT

Rationale: Hyperglycaemia predicts a poor outcome in Intensive Care Unit (ICU) patients. Whether this is true for respiratory failure necessitating non-invasive ventilation (NIV) is not known.

Objectives: To determine whether hyperglycaemia within 24 h of admission independently predicts outcome of NIV during acute decompensated ventilatory failure complicating chronic obstructive pulmonary disease (COPD) exacerbations.

Methods: Patients with COPD presenting with acute hypercapnic respiratory failure at University Hospital Aintree between June 2006 and September 2007 and receiving NIV within 24 h of admission were studied prospectively. Random blood glucose levels were measured before NIV administration.

Results: 88 patients (mean baseline pH 7.25, $PaCO_2$ 10.20 kPa, and PaO_2 8.19 kPa) met the inclusion criteria, with NIV normalising arterial pH off therapy in 79 (90%). After multivariate logistic regression, the following predicted outcome: baseline respiratory rate (OR 0.91; 95% CI 0.84 to 0.99), random glucose ≥7 mmol/l (OR 0.07; 95% CI 0.007 to 0.63) and admission APACHE II (Acute Physiology and Chronic Health Evaluation II) score (OR 0.75; 95% CI 0.62 to 0.90). The combination of baseline respiratory rate (RR) <30 breaths/min and random glucose <7 mmol/l increased prediction of NIV success to 97%, whilst use of all three factors was 100% predictive.

Conclusions: In acute decompensated ventilatory failure complicating COPD, hyperglycaemia upon presentation was associated with a poor outcome. Baseline RR and hyperglycaemia are as good at predicting clinical outcomes as the APACHE II score. Combining these variables increases predictive accuracy, providing a simple method of early risk stratification.

Non-invasive ventilation (NIV) is an effective treatment for acute hypercapnic respiratory failure (AHRF) complicating a chronic obstructive pulmonary disease (COPD) exacerbation.[1] However, some patients do not improve with NIV and in these individuals endotracheal intubation or, where appropriate, palliation are needed. Several factors are associated with an increased risk of NIV failure. In one randomised controlled trial survival was worse when the initial pH was below 7.3, or if $PaCO_2$ or the respiratory rate (RR) failed to improve after 4 h of treatment.[2] Other factors retrospectively identified as poor prognostic markers include a high APACHE II (Acute Physiology and Chronic Health Evaluation II) score, radiologically confirmed consolidation, haemodynamic instability, impaired consciousness, the presence of comorbidities, impaired functional status and metabolic dysfunction.[3–5] NIV is now offered to patients with COPD presenting with more severe acidosis than in these early clinical trials and appears to be effective in improving clinical outcomes.[6] Whether the same risk factors operate and do so to the same degree is not clear.

In patients with a wide range of conditions admitted to intensive care, pretherapy hyperglycaemia is an independent predictor of a poor outcome[7–10] which may be improved by tight glycaemic control.[11 12] A retrospective case note review of patients hospitalised with COPD exacerbations but not necessarily exhibiting respiratory failure found an increased mortality and longer hospital stay in patients with random blood glucose of ≥7 mmol/l.[13] Whether hyperglycaemia upon presentation influences the outcome of NIV in acidotic COPD patients is not known nor is its relationship to other identified poor prognostic factors. To investigate these relationships we prospectively collected data about the occurrence of hyperglycaemia and the risk factors identified above in an observational study of consecutive patients with COPD undergoing NIV.

METHODS

Patients

All patients admitted to University Hospital Aintree between June 2006 and September 2007 with an exacerbation of COPD who received NIV within 24 h of admission to the Respiratory Failure Unit (RFU) or ICU were prospectively identified. AHRF was defined by the presence of worsening of dyspnoea and an arterial pH <7.35 with a $PaCO_2$ >6 kPa. The diagnosis of COPD was made clinically and confirmed by spirometry whenever possible.[14] Where spirometry was unavailable, a senior respiratory clinician confirmed that COPD was the most likely diagnosis based on the history, tobacco exposure, examination findings and radiology. An exacerbation of COPD was defined according to pre-existing criteria[14] while pneumonia was diagnosed when a new infiltrate on the chest radiograph occurred with one or more of the following: dyspnoea, cough, sputum production, fever >38°C, abnormal breath sounds and rales.[15] We excluded patients with other respiratory conditions—for example, chest wall and neuromuscular disease leading to acute on chronic ventilatory failure, those presenting with acute cardiogenic pulmonary oedema, those patients where doxapram was used as an adjunct to NIV, patients commenced on NIV >24 h following hospital admission and those with known active malignancy or a diagnosis of acute or chronic thromboembolic disease. In addition, patients with

COPD weaned using NIV postextubation and those unable to tolerate the mask due to agitation or claustrophobia were excluded. Details of the local protocol in our institution for administering NIV during acute exacerbations of COPD are given in the online supplement.

Protocol and measurements

Before initiating NIV, the RR was measured by a doctor, together with the arterial blood gases which were repeated at 1 and 4 h post-treatment. Details of the diagnosis, associated comorbidities, usual medication including oral corticosteroids, previous lung function and the time from presentation to the initiation of NIV were recorded together with body temperature, haemodynamic status and Glasgow Coma Score (GCS) pre-NIV. Venous blood was drawn for the measurement of the blood count (Sysmex XE-2100 automated full blood count analyser; Sysmex Milton Keynes, UK), routine biochemistry (AU 2700 automated chemistry analyser; Olympus UK, Watford, UK) and random glucose levels (hexokinase method, AU 2700 Olympus). In all episodes, blood samples were taken on admission to the Emergency Department but before NIV began—that is, the first blood glucose value that was obtained on hospital arrival was used. Hyperglycaemia was defined as a random blood glucose level $\geq$7 mmol/l.[13] The baseline APACHE II score was calculated by a single investigator (BC).[16] Preadmission comorbidity was assessed using the Charlson comorbidity index.[17] Successful NIV was defined as the resolution of respiratory acidosis leading to successful weaning from the ventilator, and no requirement for ventilatory support for at least a further 48 h. Formal ethical approval for the study was obtained via the regional ethics committee.

Statistical analysis

Statistical analysis was performed using SPSS 15.0. Data are presented as mean and SD unless otherwise stated. We used the independent sample t test to identify significant differences in continuous variables between patients failing or succeeding with NIV, and the χ^2 test for categorical variables. Statistical significance was defined as a p value <0.05. No "a priori" power calculation was performed as the relationship between blood glucose and NIV success in patients with COPD was not known. The statistical significance of each variable in predicting the outcome from NIV was initially determined using univariate logistic regression. Subsequently, baseline variables with a p value <0.1 were included in a multivariate logistic regression model which identified the most parsimonious predictors of NIV outcome. The variables identified from the logistic regression model were used to construct receiver operating characteristic (ROC) curves from which we determined the sensitivity, specificity, and positive and negative predictive value of these factors. Candidate variables were considered in isolation and in combination to establish whether they added additional explanatory power to this analysis.

RESULTS

Of 168 patients receiving NIV for decompensated AHRF, 109 episodes in 92 patients fulfilled the study entry criteria. Two patients were excluded due to claustrophobia and agitation during treatment, leaving 107 episodes in 90 patients (fig 1). Thirteen patients presented with more than one episode of AHRF during the study period comprising 17 such episodes in total. For those patients presenting with more than one episode of AHRF during the study period, the first episode was used for the purposes of the study, leaving 90 episodes in 90 patients. Random blood glucose data were available in 88 of these 90 patients, thus leaving 88 episodes in 88 patients for final analysis.

The ceiling of treatment was set at NIV alone in 73% (64/88) of patients. NIV failed in 16 patients (18%), one patient who received invasive ventilation surviving to discharge while the remaining 15 patients died, all of whom had NIV as their ceiling of treatment. In 11 (12%) patients, COPD exacerbation was associated with pneumonia but the mortality was not worse in this subgroup ($p = 0.12$). NIV was administered in the RFU in 86 patients and in the ICU for the remaining 2 patients.

The baseline demographics of the study population are outlined in table 1. Spirometry data confirming the diagnosis of COPD were available for 82 (93%) patients, all recordings being within a year of the index admission. Details of the six cases where COPD was diagnosed clinically are provided in the online supplement. In 16 patients (18%), oral corticosteroids were taken before admission. Intravenous aminophylline was administered in 24 patients and this did not affect the outcome of NIV (3 NIV failures received aminophylline $p = 0.54$; non-significant).

Glycaemia and outcome of NIV

The relationship between hyperglycaemia and outcome from NIV is summarised in table 2. Hyperglycaemia was present at baseline in 50% (44/88) of patients whilst 16 (18%) had a pre-existing diagnosis of diabetes mellitus. NIV failure was seen in 34% (15/44) of patients where random blood glucose was $\geq$7 mmol/l compared with 2% of the group with blood glucose $\leq$6.9 mmol/l (1/44; $p = 0.003$). The mean blood glucose level was higher in patients when NIV failed (9.03 (3.22) mmol/l vs 7.01 (2.18) mmol/l; t test; $p = 0.003$). A prior diagnosis of diabetes mellitus preadmission was not associated with failure of NIV (table 3), with the mean blood glucose in the 16 patients with diabetes being 8.03 (4.02) mmol/l compared with 7.23 (2.04) mmol/l in those without diabetes ($p = 0.25$ non-significant). Of the 44 patients with hyperglycaemia, pneumonia was noted in 7 (16%) compared with 4 patients (9%) with normoglycaemia ($p = 0.52$ non-significant).

When taking only those 82 patients where the diagnosis of COPD was confirmed by spirometry, the association between hyperglycaemia and failure of NIV remained. In this subgroup, NIV was successful in 71 patients and failed in 11. Baseline hyperglycaemia was present in 41% (29/71) of NIV successes and 100% (11/11) of NIV failures ($p<0.001$).

In 72 patients, oral corticosteroids were not taken before hospital admission and NIV succeeded in 58. In this subgroup,

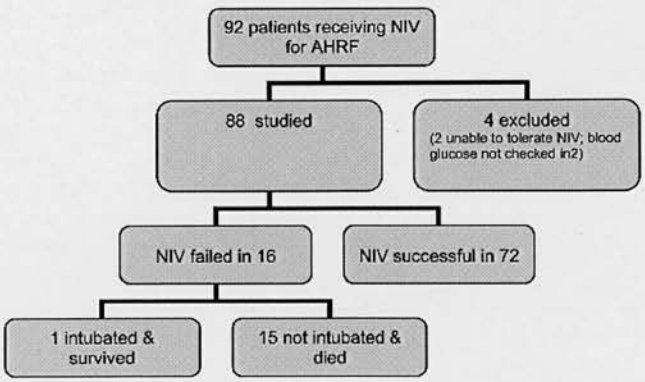

Figure 1 Flow diagram illustrating the outcome of patients receiving non-invasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF).

Table 1 Baseline demographics of the study population

Variable	Value
Age (years; mean (SD)), n = 88	70 (10)
Gender, n = 88	39 male (44%)
	49 female (56%)
FEV_1 (litres; mean (SD)), n = 82	0.68 (0.29)
FVC (litres; mean (SD)), n = 82	1.62 (0.56)
Known diagnosis of diabetes mellitus	Yes = 16 (18%; 4 prescribed insulin)
	No = 72 (82%)
Glucose level prior to NIPPV initiation, n = 88	0–6.9 mmol/l = 44 (50%)
	>7 mmol/l = 44 (50%)
Arterial pH prior to NIPPV initiation, n = 88	7.25 (0.64)
Arterial pCO_2 prior to NIPPV initiation (kPa), n = 88	10.20 (2.17)
Arterial pO_2 prior to NIPPV initiation (kPa), n = 88	8.19 (2.65)
Calculated bicarbonate (mmol/l), n = 88	25.65 (3.60)
Respiratory rate prior to NIPPV initiation (breaths/min), n = 88	27 (8)
APACHE II score prior to NIPPV initiation, n = 88	15 (4)
Charlson comorbidity index, n = 88	1.66 (0.76)

Values are given as mean (SD).
APACHE II, Acute Physiology and Chronic Health Evaluation II; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NIPPV, non-invasive positive pressure ventilation.

baseline hyperglycaemia was present in 38% (22/58) of NIV successes and 93% (13/14) of NIV failures ($p<0.001$). Hyperglycaemia was not related to prior oral corticosteroid use. Of the 16 patients prescribed oral corticosteroids preadmission, 9 (56%) presented with hyperglycaemia compared with 35 of 72 (49%) not prescribed oral corticosteroids ($p = 0.59$; non-significant).

Arterial blood gases and outcome of NIV

The relationships between the baseline pH, subsequent change in arterial blood gases over 4 h and outcome of NIV are shown in table 4 and in table 1 online. A baseline pH <7.30 before NIV did not predict NIV failure, although the relationship between outcome and presentation with a baseline pH <7.25 approached statistical significance ($p = 0.09$). In 84 patients, NIV was still being used 4 h after initiation (4 patients had died by this stage). Failure to improve arterial pH compared with baseline after 4 h NIV treatment was not associated with treatment failure nor was the inability to normalise pH following 4 h of NIV predictive.

Logistic regression analysis

Of the baseline variables tested, age, blood glucose <7 mmol/l, baseline RR, APACHE II score, mean baseline arterial pH pre-NIV and calculated serum bicarbonate level were related to the outcome of NIV treatment in the univariate logistic regression (see tables 3, 4). These variables were included in the multivariate model which identified three statistically significant predictors of NIV outcome: baseline RR (OR 0.91; 95% CI 0.84 to 0.99), random glucose ≥7 mmol/l (OR 0.07; 95% CI 0.007 to 0.63) and APACHE II score on admission (OR 0.75; 95% CI 0.62 to 0.90). The model correctly classified 93% of the successful outcomes in the sample.

The correlation between random blood glucose and the other statistically significant associations identifying NIV outcome in the univariate analysis are shown in tables 2 and 3 online. Statistically significant correlations were noted between blood glucose concentration, RR and pre-NIV pH in those patients where NIV was successful, and with baseline APACHE II score and pre-NIV pH where NIV failed. The correlations between

Table 2 Relationship between glycaemia and outcome from NIV

Random blood glucose quartile (mmol/l)	NIV success (no. of cases)	NIV failure (no. of cases)
0–6 (n = 28)	27 (96%)	1 (4%)
6–6.9 (n = 16)	16 (100%)	0 (0%)
7–8.9 (n = 26)	17 (65%)	9 (35%)
>9 (n = 18)	12 (67%)	6 (33%)

NIV, non-invasive ventilation.

baseline RR and APACHE II index and with pre-NIV pH were 0.25 ($p = 0.01$) and −0.16 ($p = 0.14$, non-significant), respectively, in the whole cohort.

To investigate further the discriminatory power of the three variables, ROC curves were constructed between RR, APACHE II index, blood glucose level and the outcome of NIV. For baseline RR and NIV outcome, the lines for sensitivity and specificity intersected at an RR of 30/min (area under the curve 0.78; 95% CI 0.62 to 0.94). In terms of APACHE II index, the point of intersection occurred at 16.5 (area under the curve 0.79; 95% CI 0.66 to 0.91), and with random blood glucose level (area under the curve 0.76; 95% CI 0.63 to 0.89) the point of intersection was at 7.3 mmol/l. The sensitivity, specificity, and positive and negative predictive value of these factors in predicting a successful outcome is shown in table 4 online. The combination of baseline RR <30 breaths/min and random glucose <7 mmol/l increased the prediction of a successful outcome from NIV to 97%, while the use of all three factors was 100% predictive in this population.

DISCUSSION

NIV represents a significant advance in the management of acute respiratory failure in patients with severe COPD. The data in our observational prospective cohort study support this, with >80% of patients recovering from an episode which a decade ago would have required invasive ventilation. This success rate is comparable with that previously reported from an ICU[18] and was not substantially different from a more mixed population of patients, many without acidosis, admitted to UK hospitals.[19] Patients with COPD managed with invasive ventilatory support are more likely to die from non-pulmonary causes than respiratory causes.[20] In surgical and medical intensive care practice hyperglycaemia is a known adverse prognostic marker.[7 21 22] Specific data about hyperglycaemic patients managed with NIV are limited. A small study suggested that "late failure" defined by deteriorating gas exchange was more frequent in patients with an initially raised blood sugar.[3] A larger but retrospective review of a mixed population of unselected patients with COPD noted longer hospital stays and greater mortality in patients presenting with hyperglycaemia. However, it was not possible to adjust for the potential confounding effects of corticosteroids while many of the diagnoses were based on purely clinical grounds.[13]

Our study in a well defined patient population found that hyperglycaemia, even when defined at only one time point, related to the final outcome irrespective of the diagnosis of diabetes, use of insulin or prior oral corticosteroid use. In general the degree of hyperglycaemia observed was modest but it may still reflect the significant physiological stress associated with deteriorating gas exchange and worsening lung mechanics, often accompanied by pulmonary infection. Some patients had radiological evidence of pneumonia, but this did not explain the occurrence of hyperglycaemia in most patients nor did it predict

Table 3 Clinical variables and outcome from NIV: univariate analysis

	NIV success (n = 72)	NIV failure (n = 16)	OR (95% CI)	p Value
Age, n = 88*	68 (10)	77 (9)	0.9 (0.84 to 0.97)	0.006
Gender, n = 88†	M = 34	M = 5	1.97 (0.62 to 1.97)	0.25 (NS)
	F = 38	F = 11		
Smoking status, n = 88†	Ex = 37	Ex = 10	0.57 (0.19 to 1.72)	0.32 (NS)
	Current = 35	Current = 6		
FEV_1 (litres), n = 82*	0.69 (0.30)	0.60 (0.17)	4.53 (0.19 to 106.4)	0.35 (NS)
FVC (litres), n = 82*	1.67 (0.55)	1.35 (0.48)	3.64 (0.73 to 18.07)	0.11 (NS)
Diagnosis of diabetes mellitus, n = 16†	12	4	0.6 (0.17 to 2.18)	0.44 (NS)
Glucose ⩾7 mmol/l, n = 88†	Glucose ⩾7 mmol/l = 29	Glucose ⩾7 mmol/l = 15	0.05 (0.006 to 0.36)	0.003
	Glucose <7 mmol/l = 43	Glucose <7 mmol/l = 1		
Time from admission to NIV administration (h), n = 88*	4.68 (4.76)	3.59 (3.85)	1.07 (0.92 to 1.24)	0.40 (NS)
IPAP (cm H_2O), n = 88*	15.07 (2.17)	15.00 (3.29)	1.01 (0.80 to 1.28)	0.34 (NS)
EPAP (cm H_2O), n = 88*	5.24 (1.38)	5.63 (1.78)	0.84 (0.58 to 1.2)	0.16 (NS)
APACHE II, n = 88*	14.63 (3.80)	19.19 (4.31)	0.76 (0.65 to 0.89)	0.001
Oral corticosteroid administered prior to admission, n = 16†	14 (19%)	2 (13%)	1.69 (0.34 to 8.31)	0.52 (NS)
Charlson comorbidity index, n = 88*	1.62 (0.73)	1.88 (0.93)	0.78 (0.35 to 1.25)	0.20 (NS)
GCS, n = 88*	14 (1)	13 (3)	1.21 (0.93 to 1.45)	0.18 (NS)
Pneumonia cases, n = 11†	7	4	0.32 (0.08 to 1.28)	0.12 (NS)
Baseline RR (breaths/min), n = 88*	26 (6)	34 (10)	0.86 (0.79 to 0.94)	0.001

Values are given as mean (SD).
*t test.
†χ^2 test.
APACHE II, Acute Physiology and Chronic Health Evaluation II; EPAP, expiratory positive airway pressure; F, female; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GCS, Glasgow Coma Score; IPAP, inspiratory positive airway pressure; M, male; NIV, non-invasive ventilation; NS, non-significant; RR, respiratory rate;

NIV failure. Thus, in our data initial hyperglycaemia had an independent prognostic value.

Initial observational data suggested a relationship between the severity of acidosis and the outcome of AHRF in COPD, a finding supported by subsequent randomised studies.[2 23] Our mean baseline pH was <7.25 in 42% of patients but, unlike the earlier studies, treatment succeeded in >70% of cases. This may explain why baseline pH was a poorer discriminant in the patient population now referred for NIV. In contrast, the initial respiratory rate was a good measure of treatment response, as has been seen elsewhere.[1 2 5 24 25] A higher RR may reflect asynchrony of the patient and the ventilator, but it may also be a marker of a greater intrinsic respiratory load promoting a shortened inspiratory time and more hypercapnia.[26 27] As the respiratory muscles are unloaded by the effects of NIV, the RR can fall, the associated pulmonary hyperinflation lessens along with the work of breathing and dyspnoea improves.[27] We observed a relationship between the APACHE II score and clinical outcomes, which was unsurprising as this index incorporates several variables which independently predicted outcome. However, the APACHE II score was no better in predicting outcome in our data than simpler measures such as the initial RR.

Table 4 Outcome from NIV and relationship with arterial blood gas variables: univariate analysis

	NIV success (n = 72)	NIV failure (n = 16)	OR (95% CI)	p Value
Baseline pH, n = 88*	7.26 (0.06)	7.22 (0.08)	3.96 (1.55 to 5.07)	0.02
Baseline PaO_2 (kPa), n = 88*	8.15 (2.73)	8.30 (2.31)	0.98 (0.80 to 1.20)	0.87 (NS)
Baseline $PaCO_2$ (kPa), n = 88*	10.20 (2.19)	10.20 (2.16)	0.99 (0.78 to 1.28)	0.99 (NS)
Baseline calculated bicarbonate (mmol/l), n = 88*	26.09 (3.44)	23.51 (3.69)	1.24 (1.04 to 1.45)	0.014
1 h pH, n = 88*	7.29 (0.06)	7.25 (0.09)	1.78 (0.04 to 2.23)	0.03
1 h $PaCO_2$ (kPa), n = 88*	8.84 (2.21)	9.50 (2.61)	0.88 (0.68 to 1.15)	0.36 (NS)
1 h PaO_2 (kPa), n = 88*	8.77 (2.87)	7.85 (1.64)	1.27 (0.84 to 1.91)	0.26 (NS)
4 h pH, n = 84*	7.32 (0.51)	7.28 (0.90)	4.34 (2.90 to 5.89)	0.14 (NS)
4 h PaO_2 (kPa), n = 84*	8.37 (2.39)	7.70 (1.22)	1.27 (0.79 to 1.96)	0.31 (NS)
4 h $PaCO_2$ (kPa), n = 84 *	8.19 (1.98)	8.47 (2.07)	0.93 (0.68 to 1.27)	0.66 (NS)

Values are given as mean (SD).
*t test.
NIV, non-invasive ventilation; NS, non-significant.

Multivariate logistic regression analysis identified three factors which explained almost all the variance in outcome in our patient group and which were largely independent of each other. ROC curve analysis defined threshold values in this population, which agreed with the conventional level of elevated blood glucose in the case of hyperglycaemia and which independently identified an RR of 30/min, the same value used in the highly discriminant CURB65 score for pneumonia severity.[28] The relative simplicity with which these variables can be measured suggests that a simple prognostic index can be developed based on these factors if our findings are validated in other trials. The presence of RR <30 combined with normoglycaemia prior to the initiation of NIV carried a specificity of 92% in predicting success from NIV with a sensitivity of 79%. When baseline RR <30 was combined with normoglycaemia and APACHE II index ⩽16, the specificity increased to 100%. In essence, the combination of these "favourable" criteria in a patient with COPD with decompensated ventilatory failure prior to initiation of NIV predicts a successful outcome. On the other hand, in terms of predicting failure of NIV, the presence of an RR ⩾30/min coupled with hyperglycaemia carried a negative predictive value of 97% and a sensitivity of 92% (the failure rate was 55% in this subgroup). We therefore conclude that the presence of these "unfavourable" criteria in a patient at baseline does not imply NIV will definitely fail but such patients may require more intensive and aggressive monitoring as there is a significantly higher risk of treatment failure in such circumstances. Validation of this model in terms of predicting outcome from NIV in acute decompensated ventilatory failure is required in a second cohort of patients.

Our study has some limitations. Although it was a prospective study, we recorded only one blood glucose value and this may vary during an acute illness. However, the use of a threshold value close to the upper limit of normal had significant discriminatory power when used as a binary outcome for NIV success. Furthermore, the timing of the measurement was similar in all cases—that is, upon presentation to hospital but prior to NIV initiation. In addition, the overall sample size of the study was small but did comprise a relatively homogenous population. We had limited information about the role of infection in these patients, but again the predictive variables selected are indirectly linked to the consequences of infection. In our cohort, acute NIV carried a relatively low failure rate of 18%. This may reflect the patient selection criteria used—that is, only patients with COPD receiving NIV within 24 h of hospital admission were included. Patients developing decompensated ventilatory failure after a longer hospitalisation or when complicated by a hospital-acquired infection probably represent a sicker group carrying a higher failure rate. Our failure to identify an association with baseline pH may reflect this focused entry criterion, although the absolute values are rather lower than in several other series. The high mortality in patients who failed NIV may reflect both the severity of the initial presentation and also current UK practice towards additional supportive ventilation which continues to be a topic for debate.[29] Our data relate to the first episode on an admission when the patient was ventilated and to the outcome of that episode. One individual who recovered from such an episode subsequently died before discharge, but overall our mortality is in keeping with other recent reports in the literature.[6 30] Although not all patients had spirometrically confirmed COPD, the predictive value of hyperglycaemia remained even after excluding those cases where spirometry was not performed. Certain factors known to affect tolerance to NIV were not measured, such as the degree of mask leak, the presence of secretions and the ability to remove them. Further research in these important areas is needed.

In summary, when patients with COPD develop decompensated ventilatory failure, baseline hyperglycaemia identifies patients with the greatest risk of failure with NIV, as does an elevated RR and increased APACHE II index on admission. Combining these approaches should provide a relatively simple way of stratifying risk and adjusting management accordingly. The RR remains an underused measurement which tracks the patient's progress. Whether changes in blood glucose during therapy are as helpful remains to be studied. Tight glycaemic control has its advocates,[11 12] but careful prospective studies will be needed before this approach can be recommended in the care of patients with primary respiratory problems treated with NIV.

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Pulmonary puzzle

Cough, confusion and flaccid paralysis in a 46-year old man with left apical consolidation and ring-enhancing lesions on cerebral imaging

CLINICAL PRESENTATION

A 46-year-old man was admitted with confusion and lower limb weakness that had developed over 2 weeks. A history of chronic productive cough was noted. Significantly, 4 years previously he had been investigated for cough and left apical lung consolidation. No evidence of *Mycobacterium tuberculosis* was found at the time and this was not investigated further. The only other relevant history was of heavy ethanol intake and self-neglect.

The patient was febrile (38.6°C), confused and unwell. He had evidence of finger clubbing, poor oral hygiene and signs of consolidation in the left lung. Early bilateral papilloedema and a flaccid paralysis in the lower limbs were noted. Admission investigations identified a raised white cell count of 21.5×10^9/l (neutrophils 19.5). Multiple sputum cultures were negative. There was no reaction to a Mantoux (5 units PPD) test. Antibodies to HIV were not detected. A chest radiograph (fig 1) and CT scan showed left apical consolidation and volume loss. A CT scan of the brain (fig 2) showed two ring-enhancing lesions in the right frontoparietal lobe. An MRI scan revealed a ring-enhancing lesion in the lumbar spine.

Craniotomy and excision of a cerebral lesion was performed, with concurrent bronchoscopy and bronchoalveolar lavage (BAL). The airways were inflamed with inspissated yellow secretions visible on the left. Histological examination of the cerebral biopsy specimen was consistent with a cerebral abscess, but no granulomatous inflammation was identified. All cultures from the BAL fluid and cerebral abscess were negative.

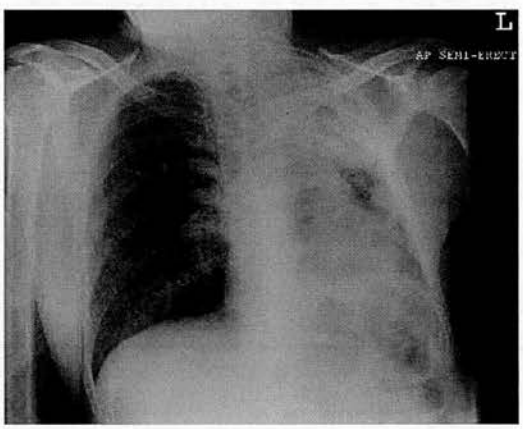

Figure 1 Chest radiograph showing left apical consolidation, volume loss and pleural thickening.

Figure 2 CT scan of the brain showing ring-enhancing lesions in the right frontoparietal lobe with surrounding oedema and mass effect.

QUESTION

What further diagnostic technique may aid in pathogen identification?

See page 920.

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Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD

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Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial

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Summary

Background The role of oral corticosteroids in treating patients with exacerbations of chronic obstructive pulmonary disease (COPD) remains contentious. We assessed in a prospective, randomised, double-blind, placebo-controlled trial the effects of oral corticosteroid therapy in patients with exacerbations of COPD requiring hospital admission.

Methods We recruited patients with non-acidotic exacerbations of COPD who were randomly assigned oral prednisolone 30 mg once daily (n=29) or identical placebo (n=27) for 14 days, in addition to standard treatment with nebulised bronchodilators, antibiotics, and oxygen. We did spirometry and recorded symptom scores daily in inpatients. Time to discharge and withdrawals were noted in each group. We recalled patients at 6 weeks to repeat spirometry and collect data on subsequent exacerbations and treatment. Hospital stay was analysed by intention to treat and forced expiratory volume in 1 s (FEV_1) according to protocol.

Findings FEV_1 after bronchodilation increased more rapidly and to a greater extent in the corticosteroid-treated group: percentage predicted FEV_1 after bronchodilation rose from 25·7% (95% CI 21·0–30·4) to 32·2% (27·3–27·1) in the placebo group ($p<0·0001$) compared with 28·2% (23·5–32·9) to 41·5% (35·8–47·2) in the corticosteroid-treated group ($p<0·0001$). Up to day 5 of hospital stay, FEV_1 after bronchodilation increased by 90 mL daily (50·8–129·2) and by 30 mL daily (10·4–49·6) in the placebo group ($p=0·039$). Hospital stays were shorter in the corticosteroid-treated group. Groups did not differ at 6-week follow-up.

Interpretation These data provide evidence to support the current practice of prescribing low-dose oral corticosteroids to all patients with non-acidotic exacerbations of COPD requiring hospital admission.

Lancet 1999; **354:** 456–60
See Commentary page xxx

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Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of death worldwide and exacerbations of this disease commonly lead to hospital admission (1250 per year in our 350 000 health district) and increased cost. The treatment of exacerbations of COPD is controversial. Guidelines[1,2] have made recommen-dations about prescribing, but although there are clear indications for antibiotic and bronchodilator use, they state that the use of oral corticosteroids is based on common practice and is not evidence based.

When given to stable COPD patients, systemic corticosteroids significantly increase the forced expiratory volume in 1 s (FEV_1) in only 10% of cases,[3] whereas inflammatory-mediator production is not influenced by this treatment.[4] Moreover, continued use of oral corticosteroids in COPD patients is associated with corticosteroid myopathy,[5] which may be potentially important for patients with frequent exacerbations who are treated with these drugs.

Several studies have investigated the outcome of systemic use of corticosteroids in exacerbations of COPD with conflicting results. One study of 96 patients suggested that there was no effect of methylprednisolone in preventing admission to hospital after 5 h treatment in the emergency room,[6] although a later, randomised double-blind study found that the readmission rate was lower in patients given treatment.[7] In a randomised controlled trial, Albert and colleagues[8] noted significant improvements in FEV_1 before bronchodilation in the first 3 days of admission in 22 patients given intravenous methylprednisolone, but improvements in FEV_1 after bronchodilation were less obvious. In another randomised controlled trial, 27 patients fit enough for discharge from the emergency room were followed up.[9] The 13 treated patients showed greater improvement in FEV_1 and the partial pressure of oxygen in arterial blood than did the 14 untreated patients. The Veterans Affairs Cooperative study group has completed a study of the effects of high-dose systemic corticosteroids on exacerbations of COPD.[10] The primary endpoint was treatment failure, rates of which were significantly lower in the glucocorticoid-treated groups than in the placebo group.

Most COPD patients admitted with exacerbations in the UK, New Zealand, and Australia[11-13] are treated with 30–40 mg oral prednisolone. We investigated the hypothesis in a prospective, randomised, double-blind, placebo-controlled trial that in more severe patients, oral corticosteroids administered in these doses would not modify the rate of improvement of lung function or significantly affect the course of hospital stay.

Patients and methods

Patients

Patients with a diagnosis of COPD presenting to the accident and emergency department of University Hospital Aintree, Liverpool,

were eligible for entry into the study if they had a history of increased breathlessness and at least two of the following symptoms for 24 h or more: increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze. We included patients who were aged 40–80 years, had a history of at least 20 pack-years of cigarette smoking, and had physiological evidence of airflow limitation with initial FEV_1 less than 70% predicted and FEV_1/forced vital capacity ratio less than 75%.[1]

We excluded patients if they had a personal or family history of asthma or atopy, uncontrolled left-ventricular failure, clinical or radiological evidence of pneumonia, received oral corticosteroids within 1 month of presentation, or if arterial blood pH on admission was less than 7·26. All patients gave written informed consent to participate, and the study was approved by the district ethics committee.

Study design

One investigator (LD) took a detailed medical history and examined patients at admission. The investigational protocol was started within 3 h of presentation to the accident and emergency department. Patients received standard treatment with nebulised β-agonist (5 mg salbutamol) and an anticholinergic (500 μg ipratropium bromide) every 6 h, controlled oxygen therapy, and oral or intravenous antibiotics at the judgment of the admitting physician. Any patient who was receiving inhaled corticosteroid therapy before randomisation was continued on this therapy. In addition, we randomly assigned patients 30 mg prednisolone every day for 14 days or identical placebo. Randomisation was done by the hospital pharmacy according to a table of random numbers. Packages of treatment were numbered in advance and used consecutively. All patients, investigators, respiratory physicians, technicians, and other hospital staff were masked to treatment status until the end of the study. Study duration was from the time of admission to the time of discharge and included a follow-up visit 6 weeks after admission.

On admission, we took blood samples for full blood count, including absolute eosinophil count, and arterial blood gas measurement. Sputum was collected for microscopy, culture, and sensitivity. Spirometry was done daily from admission, before, and 15 min after 5 mg nebulised salbutamol, by a dry-bellows spirometer that met the American Thoracic Society and British Thoracic Society standards.[14] At least three forced expiratory manoeuvres were obtained on each occasion until two were within 5%. We compared airflow measurements with European Steel and Coal Company predicted values.[15] We obtained a daily symptom score, which was calculated from a diary completed by the patient. Questions were asked about breathlessness, sputum production, wheeze, mobility, sleep quality, cough, and general well-being. Patients were asked to score each of the symptoms from 0 (much better than usual) to 5 (much worse than usual). We also collected data about potential side-effects of oral corticosteroids (mood swings, heartburn, and overt gastrointestinal bleeding), and tested patients' urine daily for glucose.

On day 5, static lung volume was measured by helium dilution, and transfer factor by single-breath method (Benchmark respirometer, PK Morgan, Rainham, Kent, UK). We did skin tests to eight common allergens. Also on day 5, we used the St George's respiratory questionnaire to assess patients' usual health status.[16] Patients were asked, "Ignoring this admission, how has your health been over the last 6 months?" and were shown a 200 mm visual analogue scale with markings every 20mm from 0 (could not have been worse) to 10 (perfect health) and asked to point to the number that they felt best answered the question.

The respiratory physicians in charge of the patients, who were not investigators, were free to withdraw patients from the study at any time if they felt clinical improvements were not satisfactory. We automatically withdrew any patient whose arterial blood pH fell below 7·26 and treated them with oral corticosteroids and supportive therapy as required. Patients were free to withdraw at any time if they were not satisfied with their progress. The physicians in charge also decided the time at which patients reached medical fitness for discharge, and it is this date that we have used. In some patients, the actual time to discharge was delayed because of social and transport arrangements. On the day of discharge, a second visual analogue score was recorded for the answer to, "How do you feel today compared to the day of admission?" from 0 (very much worse) to 10 (very much better).

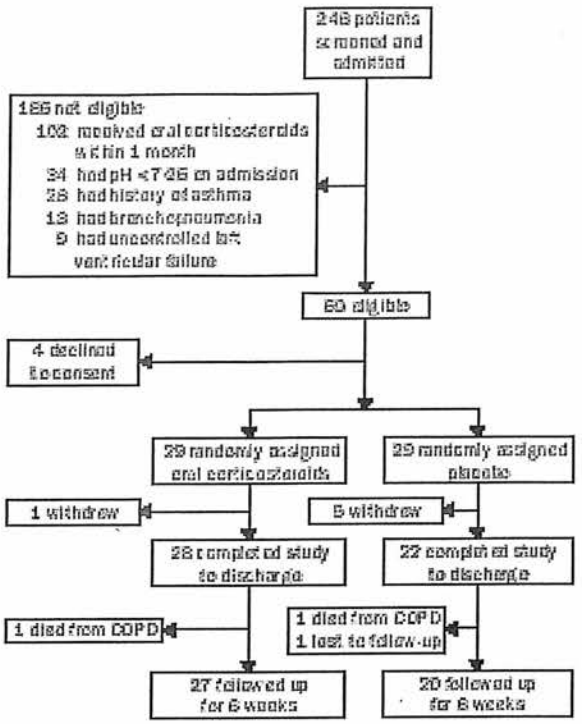

Figure 1: **Trial profile**

At 6 weeks after admission, we recalled patients to repeat spirometry before and after 5 mg nebulised salbutamol and to complete a second St George's respiratory questionnaire and visual analogue scale score of health perception over the past 6 months. We collected data about treatment at follow-up and whether patients had required treatment for further exacerbations from their family physician or the hospital since discharge.

Statistical analysis

We calculated that a sample size of 27 in each group would give us 80% power to detect a difference of 0·05 L per day in mean slope between the groups, with an SD of 0·0625. All data were analysed with Microstat version 1 and SPSS version 8.0. We calculated means (SE), and used Student's t test, ANOVA, and ANCOVA to compare normally distributed data, and Wilcoxon's rank and χ^2 tests to compare non-normal data.

Results

We screened 246 patients for the study, and 60 met the inclusion criteria (figure 1). The most common reason for exclusion was previous treatment with oral corticosteroids before attending the accident and emergency department. Of the four patients refusing consent, three declined because they refused oral corticosteroids after being told of possible side-effects and one because she did not wish to participate in a clinical trial.

29 patients were randomly assigned active treatment and 27 were assigned placebo. Six patients were withdrawn from the study: five in the placebo group (on days 1, 2, 3, 6, and 13) and one in the corticosteroid-treated group (day 11). Only one patient (on placebo) was

Characteristics	Completed the study (n=50)	Withdrawn (n=6)
Age (years)	67 (1·2)	64 (3·6)
Sex		
Male	34 (68%)	5 (83%)
Female	16 (32%)	1 (17%)
Smoking history		
Current smokers	26 (52%)	3 (50%)
Pack-years	55 (5)	56 (7)
Eosinophil count (×10⁹/L)	0·18 (0·03)	0·09 (0·03)
Symptom score on admission	26·7 (0·7)	30·5 (0·7)
SGRQ on day 5	72·6 (2·4)	68·5 (7·0)
Percentage predicted FEV_1		
On admission, before bronchodilation	24·7 (1·8)*	10·2 (3·8)
On admission, 15 min after bronchodilation	27·1 (1·7)†	14·1 (3·5)
On discharge, before bronchodilation	35·1 (2·0)	32·5 (4·2)
On discharge, 15 min after bronchodilation	37·4 (2·1)	31·4 (4·7)
On day of withdrawal, 15 min after bronchodilation	..	10·7 (4·3)
1 day after withdrawal, 15 min after bronchodilation	..	23·7 (2·9)

SGRQ=St George's respiratory questionnaire. Values are means (SE) or numbers (%). Patients withdrawn had significantly worse spirometry on admission than those completing study. *p=0·008. †p=0·004.

Table 1: **Baseline characteristics of patients**

withdrawn because of respiratory acidosis. During week 1 of the study, patients in the placebo group were significantly more likely to be withdrawn than those in the active-therapy group (p=0·034). Patients withdrawn from the study had significantly lower percentage predicted FEV_1 on admission before (p=0·008) and after bronchodilation (p=0·004) than those completing the study, but other baseline characteristics did not differ (table 1).

Of the 50 patients completing the study, 34 were men and 16 women (mean age 67 years [SE 1·2]; mean smoking history 55 pack-years [4·5]). These patients had severe airflow obstruction with mean FEV_1 before bronchodilation 0·59 L (95% CI 0–1·2) and mean percentage predicted FEV_1 before bronchodilation 24·7% (21·2–28·2). Samples for arterial blood gas analysis were taken from all patients. In the 34 patients measured on air, mean pH was 7·33 (7·19–7·47), partial oxygen pressure was 8·9 kPa (8·4–9·4), partial carbon-dioxide pressure was 5·4 kPa (4·9–5·9). Arterial blood gases did not differ between the two groups. At study entry, all patients used inhaled or nebulised short-acting β-agonist therapy, 34 (64%) inhaled or nebulised anticholinergics, 45 (80%) inhaled corticosteroids, 11 (20%) oral theophyllines, eight (14%) oxygen cylinders, four (7%)

Characteristics	Oral corticosteroids (n=28)	Placebo (n=22)
Age (years)	66 (1·3)	69 (2·1)
Sex		
Male	17 (61%)	17 (77%)
Female	11 (39%)	5 (23%)
Smoking history		
Current smokers	14 (50%)	12 (55%)
Pack-years	48 (4)	64 (10)
Eosinophil count (×10⁹/L)	0·12 (0·03)	0·24 (0·06)
Symptom score	26·1 (1·1)	27·6 (0·6)
SGRQ score	75·4 (3·6)	69·1 (3·6)
FEV_1 (L)		
Before bronchodilation	0·66 (0·05)	0·58 (0·07)
After bronchodilation	0·70 (0·01)	0·70 (0·07)
Percentage predicted FEV_1		
Before bronchodilation	27·4 (2·4)	21·4 (2·5)
After bronchodilation	28·2 (2·4)	25·7 (2·4)

SGRQ=St George's respiratory questionnaire. Values are means (SE) or numbers (%).

Table 2: **Demography of patients on admission**

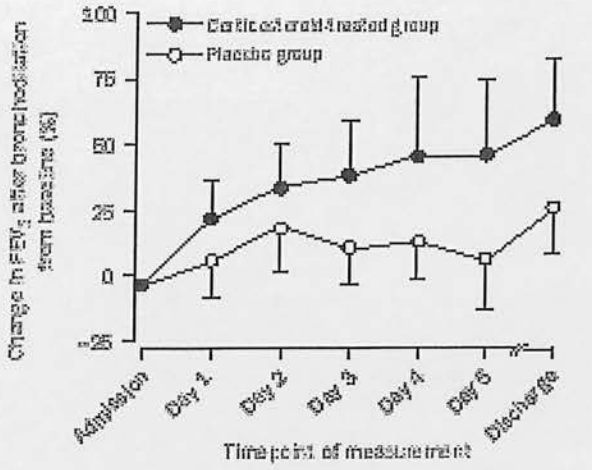

Figure 2: **Change in absolute FEV_1 after bronchodilation from admission by day of study in active and placebo groups (according to protocol)**
Means (95% CI) are shown.

long-term oxygen therapy, and two (4%) inhaled long-acting β-agonists. At study entry there were no differences in previous treatment between groups.

34 patients had purulent sputum on admission, although only 11 yielded positive cultures (seven *Haemophilus influenzae*, two *Streptococcus pneumoniae*, one *Moraxella catarrhalis*, and one *Pseudomonas aeruginosa*). 52 patients were treated with oral or intravenous antibiotics. The mean percentage predicted residual volume measured on day 5 of admission was 181·4% (SE 6·8), total lung capacity 112·3% (2·0), and single-breath diffusing capacity 65·3% (3·4), and there were no differences between groups. No patient had a positive skin test. There were no deaths during admission. 28 patients on oral corticosteroids and 22 on placebo completed the study to the time of discharge, but two died before the 6-week follow-up visit. Characteristics did not differ between groups on admission (table 2).

By the time of discharge, percentage predicted FEV_1 before bronchodilation had risen from 21·4% (95% CI 16·5–26·3) to 31·0% (26·3–35·7) in the placebo group (p<0·0001) and from 27·4% (22·5–32·3) to 38·4% (32·9–43·9) in the corticosteroid-treated group (p<0·0001). Percentage predicted FEV_1 after bronchodilation rose from 25·7% (21·0–30·4) to 32·2% (27·3–37·1) in the placebo group (p<0·0001) and 28·2% (23·5–32·9) to 41·5% (35·8–47·2) in the corticosteroid-treated group (p<0·0001). Changes in FEV_1 after bronchodilation were significantly greater in the corticosteroid-treated group (figure 2) and these changes were similar to values before bronchodilation. Until day 5, FEV_1 after bronchodilation increased in the corticosteroid-treated group by 90 mL per day (50·8–129·2) compared with that in the placebo group of only 30 mL per day (10·4–49·6; p=0·039). With FEV_1 after bronchodilation on admission as a covariate, the increase until day 5 in the corticosteroid-treated group remained significantly greater than that in the placebo group (p=0·048). Improvement plateaued earlier in the corticosteroid-treated group; by day 5, patients receiving corticosteroids had increased FEV_1 after bronchodilation to 92% of that achieved at discharge, compared with only 85% in the placebo group (p<0·041). Changes in forced vital capacity were similar to those seen in FEV_1.

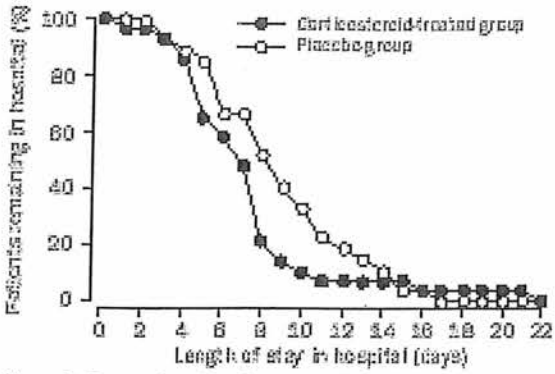

Figure 3: **Proportion of patients remaining in hospital by day of admission by treatment group (intention to treat)**

Visual analogue scale scores during the admission period rose significantly in the two groups by a mean of 2·6 (−0·5 to 5·7) in the placebo group and 3·4 (2·8–4·0) in the corticosteroid-treated group (both $p<0·0001$). Decreases in symptom scores were seen in the two groups. The greatest symptom changes were found in sleep quality, breathlessness, mobility, and general well-being, with a trend towards greater improvement in the corticosteroid-treated group. In both groups, the most striking changes in symptom scores were seen between days 0 and 1, and days 1 and 2, with a further improvement from day 2 to discharge ($p=0·01$, $p=0·005$, $p<0·0001$). There were no reports of change in mood. Three patients in the corticosteroid-treated group and two in the placebo group complained of heartburn, but there were no episodes of overt gastrointestinal bleeding. Six patients in the corticosteroid-treated group developed transient glycosuria.

Length of hospital stay was analysed by intention to treat for all 56 patients in the study. The median length of stay in patients treated with oral corticosteroids (7 days) was significantly shorter than in those receiving placebo (9 days; $p=0·027$; figure 3).

At 6 weeks, percentage predicted FEV_1 after bronchodilation was 39·6% (95% CI 32·5–46·7) in the corticosteroid-treated group and 33·2% (27·9–38·5) in the placebo group, which were not significantly different to discharge values. There was no change in St George's respiratory questionnaire or visual analogue scale scores for health perception in the past 6 months in the two groups. 16 patients had required treatment for further exacerbations of COPD, nine in the oral corticosteroid group and seven in the placebo group. 11 patients had received further antibiotics or oral corticosteroids from their family physicians, and five had required further hospital admission, during which they had also received antibiotics or oral corticosteroids. There was no difference in exacerbation rate, admission rate, or treatment received between the two groups. None of age, current smoking or ex-smoking, eosinophil count, or concurrent treatment predicted whether further exacerbations might occur within this 6-week period.

Discussion

Any treatment that can hasten the resolution and lower the costs of exacerbations of COPD[17,18] is welcomed. Data from randomised trials in outpatients suggest that oral corticosteroids can increase the rate of resolution of the attack, but data have only been seen in short-term treatment of inpatients and the impact on health costs was unclear. We found significant differences in the rate of improvement of FEV_1 before and after bronchodilation compared with placebo, which suggests that the effect of oral prednisolone was more than an indirect effect on bronchomotor tone. Hospital stays were shorter for patients treated with prednisolone than for those on placebo.

Oral prednisolone is widely prescribed for exacerbations of COPD[11-13] and was the most common reason for patients' ineligibility. Similar difficulties have been seen in other studies.[8,9] Ethical constraints prevented us from extending our study to acidotic patients, although we have no reason to suppose they would have differed in changes in FEV_1. Likewise, we were obliged by our ethics committee to offer an open trial of oral corticosteroids to all patients withdrawn. Thus, we presented hospital stay on an intention-to-treat basis, but restricted data for FEV_1 to the according-to-protocol analysis. This approach weighs against the corticosteroid-treated group because the sickest patients probably dropped out first, which would lead to a subsequent improvement in the rate of recovery in the placebo group.

We took measurements after high doses of nebulised β-agonist to follow the patients' progress. Data in similar patients suggest that nebulised β-agonist or anticholinergics are probably equally effective bronchodilators during recovery from an exacerbation.[19] Even at discharge, our 56 patients remained significantly obstructed, with a mean percentage predicted FEV_1 after bronchodilation of 37·5% (SE 2·0).

Spirometry was done more often than in the outpatient study and the rate of change of FEV_1 after bronchodilation was three times greater in the corticosteroid-treated group than in the placebo group. Maximum improvement in FEV_1 after bronchodilation was seen by day 5 in the corticosteroid-treated group, whereas time to plateau in the placebo group was significantly longer. Since the improvement reached a plateau at day 4 in the corticosteroid-treated group, the 90 mL per day value (calculated at day 5) may underestimate the rate of improvement. Similar changes were seen for forced vital capacity.

Symptom changes showed a similar time course in each group, and like the outpatients[9] showed a trend towards greater improvement in the corticosteroid-treated group that did not reach significance. This may reflect the non-parametric nature of such data, or the need for greater numbers in the trial. Both groups showed significant improvements over the admission period that did not match the changes in FEV_1, with substantial changes in general well-being, sleep quality, and mobility within 48 h of admission, and much smaller changes in perceived cough, wheeze, and sputum production.

Our patients were not only physiologically more severely affected than in other studies, but had a worse health status than patients admitted with exacerbations in other UK studies.[20,21] Although we reported similar improvements in health during admission in the two groups, this similarity did not change during the 6 weeks of follow-up; spirometry was similar at discharge. At 6 weeks the St George's respiratory questionnaire did not register any change from that completed at 5 days, which suggested that either the score changes less in more severe patients, or recovery from an exacerbation takes longer than 6 weeks to register. Although improvement in FEV_1 after bronchodilation was maintained at 6 weeks, patients

treated with corticosteroids had similar morbidity at follow-up to those receiving placebo, which suggests that with treatment at 30 mg the initial benefit does not extend beyond the early stages of recovery from an exacerbation.

Neither the mechanism of the effects of oral prednisolone nor the selection of patients most likely to benefit is clear. Despite the absence of any effect on several cytokines in stable patients,[4] other data suggest that eosinophils and neutrophils are increased in exacerbations of COPD.[22,23] No simple clinical, biochemical, or physiological marker, including duration of disease, current smoker or ex-smoker, presence or absence of acute infection, eosinophil count, and baseline FEV_1, reliably distinguished those patients who responded from those who did not. Prescription of oral corticosteroids for all patients may therefore be the most practical solution.

Our data support the current practice of prescribing low-dose oral prednisolone to patients with non-acidotic exacerbations of COPD who require admission to hospital. Benefits in spirometric improvement are clearly seen within the first 5 days and are matched by an improvement in symptoms of well-being, mobility, and sleep quality. However, the benefits do not extend beyond hospital discharge and shorter courses may be equally effective.

Contributors

P M A Calverley and R M Angus had the original idea for the study, which was developed and planned by all contributors. L Davies recruited the patients, did the clinical assessments, organised the investigations, and analysed the data. All investigators contributed to the writing and critical revision of the paper.

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Withdrawal From Treatment as an Outcome in the ISOLDE Study of COPD*

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AMERICAN COLLEGE OF CHEST PHYSICIANS®

Withdrawal From Treatment as an Outcome in the ISOLDE Study of COPD*

Peter M. A. Calverley, MD; Sally Spencer, BSc; Lisa Willits, PhD, MSc; P. Sherwood Burge, MD; and Paul W. Jones, MD; on behalf of the ISOLDE Study Group

Objectives: **To investigate the determinants of patient withdrawal from our study, and the effect of these withdrawals on the outcome of treatment with inhaled corticosteroids in patients with COPD.**
Design: **A double-blind, placebo-controlled, randomized trial.**
Setting: **Eighteen outpatient centers in the United Kingdom.**
Participants: **Seven hundred fifty-one patients with stable COPD defined clinically and as baseline postbronchodilator $FEV_1 \geq 0.8$ L and < 85% predicted, FEV_1/FVC ratio < 70%, and FEV_1 change after albuterol < 10% of predicted.**
Intervention: **Random assignment of either 500 μg bid of inhaled fluticasone propionate (FP) using a spacer device or an identical placebo inhaler. Treatment was continued for 3 years or until patients withdrew from follow-up.**
Measurements and results: **Postbronchodilator FEV_1 was measured on three occasions before randomization and every 3 months thereafter. Health status was assessed by the disease-specific St. George Respiratory Questionnaire (SGRQ) and the modified short-form 36 questionnaire (SF-36) at baseline and every 6 months. Three hundred thirty-nine patients withdrew, of whom 156 patients received FP. Prescription of frequent courses of oral prednisolone was the most common reason for withdrawing as specified in the protocol (69 patients in the FP group withdrew due to respiratory symptoms, compared with 93 patients in the placebo group). This explained the significantly greater dropout of placebo-treated patients that was most evident when FEV_1 was < 50% predicted. Patients withdrawing had a significantly more rapid decline in health status, measured by both the SGRQ and the SF-36 ($p < 0.001$). Those withdrawing from the placebo group had a more rapid decline in FEV_1 and more exacerbations than the FP-treated groups. Baseline FEV_1 was lower in dropouts than in patients completing the study receiving placebo, but there was no difference between the respective groups receiving FP.**
Conclusions: **Patients who withdrew from follow-up were those with the most rapidly deteriorating health status and lung function. Losing these patients from the final analysis can reduce the power of a study to achieve its primary end point.** ***(CHEST 2003; 124:1350–1356)***

Key words: COPD; exacerbation; fluticasone propionate; patient withdrawal

Abbreviations: FP = fluticasone propionate; ISOLDE = Inhaled Steroids in Obstructive Lung Disease; SF-36 = modified short-form 36 questionnaire; SGRQ = St. George Respiratory Questionnaire

In most areas of pulmonary medicine, treatment is based on the results of carefully conducted, randomized controlled trials. In diseases such as bronchial asthma, brief periods of follow-up are sufficient to evaluate the effect of most drugs, including those that modify the natural history of the disease.[1,2] Treatment trials commonly last from 3 to 12 months; in addition to conventional outcomes such as changes in pulmonary function, symptoms, or health status, the number of patients who withdraw from follow-up and

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Drs. Calverley, Burge, and Jones, and Ms. Spencer were all independent investigators in the ISOLDE study from which this work is derived. This study was supported by a grant from GlaxoSmithKline. Ms. Willits is a statistician working for GlaxoSmithKline. The investigators had unrestricted access to the data and determined its analysis throughout the study.

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their reasons for doing so are reported.[3,4] This patient dropout information provides further useful information about the effectiveness and acceptability of treatment.

Evaluating therapy in patients with COPD usually takes longer, although drugs such as long-acting inhaled β-agonists can modify health status within 16 weeks.[5] Changes in disease progression and, particularly in the rate of decline of FEV_1, are harder to assess, and should be monitored over at least 3 years. There is general agreement that it is difficult to do this in < 3 years, the minimum period chosen in a series of intervention studies[6–9] using inhaled corticosteroids. Maintaining follow-up over 3 years poses significant problems, as COPD is characterized by exacerbations of disease that can lead to study withdrawal from the study. Patient withdrawal due to exacerbations is a particular problem when studying inhaled corticosteroids, as courses of oral corticosteroids are the most effective way of speeding the resolution of exacerbations[10,11]; however, if these courses are administered frequently, the outcome of the trial may be affected.

Patient withdrawal is not a problem when patients are studied early in the natural history of the disease when exacerbations are infrequent.[6,7] The Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study recruited patients with established disease. To show a treatment effect, it was important to retain the patients within the trial for as long as possible. The intention-to-treat analysis of this study has now been reported.[8] In this article, we examine the characteristics of those patients who withdrew from the trial, and the effect the withdrawals had on our study population and how we analyzed the data. We believe that these data are relevant to future investigators who study patients of a similar severity, in which patient behavior during long-term follow-up can be very different from patients with milder disease.

Materials and Methods

Patients

Details of the trial design and patient recruitment have been presented previously.[8] All patients had a clinical diagnosis of nonasthmatic COPD, met the established diagnostic criteria for this disorder,[12,13] were aged 40 to 75 years inclusive, and had a history of current or previous smoking. At baseline, postbronchodilator (400 μg albuterol) FEV_1 was ≥ 0.8 L and < 85% predicted, (FEV_1/FVC) ratio was < 70%, and the FEV_1 change after albuterol was < 10% of predicted. Patients with a clinical diagnosis of asthma, those requiring any nontrial anti-inflammatory treatment for lung disease or β-adrenergic blockers, patients with a life expectancy < 5 years due to concomitant disease, and those unable to meet the required standards for spirometry at the pretrial visit were excluded. Nasal and ocular topical corticosteroids were allowed, as were methylxanthines and long-acting inhaled bronchodilators. All patients received albuterol, 200 μg, and ipratropium bromide, 80 μg, as required throughout the trial. The protocol was approved by the ethical review committee of each participating center, and all subjects gave written informed consent.

Spirometric Measurements (FEV_1 and FVC)

Measurements were made at the same time of day for each subject. Short-acting bronchodilators were withheld for 4 h, oral or long-acting bronchodilators for 12 h, caffeine-containing products for 4 h, smoking for 2 h, and large meals for 1 h prior to spirometric measurements. Measurements were made with patients in the seated position after 15 min of resting. Spirometry was performed before bronchodilation, and then 30 min after treatment with 80 μg of ipratropium bromide and 400 μg of albuterol.

Health Status Measurement

The St. George Respiratory Questionnaire (SGRQ) is a supervised self-administered measure, designed specifically for use in airways disease.[14] It is a 50-item survey from which a total of three component scores are calculated: symptoms (distress caused by specific respiratory symptoms), activity (physical activities that cause or are limited by breathlessness), and impacts (social and psychological effects of the disease). The SGRQ is scored from 0 to 100, where 0 indicates best health and 100 indicates worst health. A change in score of 4 U is consistent with a clinically significant change in the patient[15,16]; therefore, an increase in score indicates worsening health status. The SGRQ has been shown to be a valid measure of health impairment in patients with chronic airflow limitation, and to respond to change with therapy.[5,14,17]

General health status was assessed using the SF-36, a core generic measure.[18] It is a self-completed questionnaire containing 36 questions covering eight health concepts: physical function, physical role limitation, mental role limitation, social function, mental health, pain, energy/vitality, and health perception. Two summary components (physical and mental) can also be calculated by differentially weighting the scales. The SF-36 scales are scored as a percentage of impairment, with 0 representing worst health and 100 indicating best health. With this scale, a decrease in score indicates worsening general health. Its reliability is extensively documented.[19]

Other Baseline Measurements

Smoking history was validated with exhaled breath carbon monoxide and urinary cotinine measurements. Smokers were defined as those currently smoking or with a urinary cotinine level > 40 ng/mL. Ex-smokers were those who had given up smoking, and had a urinary cotinine level < 40 ng/mL Gas transfer was measured using the single-breath method. Skin-prick tests with diluent control, 10% histamine, and allergen extracts of *Dermatophagoides pteronyssinus*, cat dander, mixed grass pollens, and *Aspergillus fumigatus* were read at 15 min. Maximum wheal diameters were measured, and atopy was defined as a > 3 mm-wheal to at least one allergen extract with appropriate controls.

Protocol

After completing an 8-week run in period to establish clinical stability and confirm the postbronchodilator spirometry values on

three occasions, patients were offered a 2-week trial of oral corticosteroids (0.6 mg/kg/d) prior to commencing 3 years of trial medication. Treatment was randomized between 500 μg of fluticasone propionate (FP) or an identical placebo bid from a metered-dose inhaler using a Volumatic spacer device (Allen and Hanbury; Greenford, Middlesex, UK). The patients re-attended were followed at 3-month intervals when postbronchodilator spirometry was recorded, and every 3 months thereafter together with a detailed account of all new symptoms and disease exacerbations. These exacerbations were defined as worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics and/or oral corticosteroids. Health status was recorded at baseline and every 6 months thereafter.

Criteria for Withdrawal

Patients were permitted to withdraw at any time during the study at will or at the discretion of their physician. Reasons for withdrawal were categorized into those that were respiratory and related to the underlying COPD and into other medical and social reasons leading to the discontinuation of follow-up. Patients who were treated by their family physician with a course of oral corticosteroids on three occasions during any 3-month period were withdrawn as per protocol, automatically considered as a study dropouts, and offered open-label therapy with inhaled corticosteroids. Further follow-up of these patients was not undertaken.

Data Analysis

Patients in whom 3 years of follow-up data were available from the time of randomization were considered to be completers; all other randomized patients were classified as noncompleters. Student *t* tests were used to analyze differences in mean values between treatment groups. A Kaplan-Meier plot was used to compare the time to withdrawal between treatment groups. The Fisher exact test compared treatment withdrawals by baseline FEV_1. A random coefficients hierarchical model, described elsewhere,[8] was used to determine the rates of change in FEV_1 and health status for patients who completed the study and those who withdrew. Data are expressed as mean (SD) unless stated otherwise stated. Baseline FEV_1 is the mean of data measured at 4 weeks and 8 weeks of the run-in period. Tests were two sided, with a 15% level of significance to take into account multiple comparisons.

RESULTS

Demographic and Baseline Characteristics

The demographic and baseline characteristics of the patients categorized into those completing and withdrawing and by treatment allocation are presented in Table 1. At the beginning of the study, there were no significant differences in gender, atopy, smoking status, or pack-years of tobacco exposure between any of these groups; however, patients who withdrew while receiving placebo were significantly more likely to have been receiving inhaled corticosteroids before entry into the trial. The baseline FEV_1 data did not differ between patients who did and did not withdraw in the FP group, but was lower in those withdrawing from placebo. This was different at the 5% significance level, but did not meet our *post hoc* criterion for statistical significance.

Reasons for and Time to Withdrawal

Of the 751 patients randomized, 402 patients successfully completed the 3-year follow-up, of whom 220 patients had received inhaled FP. The most common reasons for withdrawal were respiratory events (n = 69, FP group; n = 93, placebo group), the majority being frequent exacerbations as

Table 1—*Demographic and Baseline Characteristics

Characteristics	FP (n = 376)		Placebo (n = 375)	
	Completed 3 yr (n = 220)	Withdrawn Prior to 3 yr (n = 156)	Completed 3 yr (n = 182)	Withdrawn Prior to 3 yr (n = 193)
Age, yr	63.2 (6.8)	64.5 (7.5)	62.8 (7.1)	64.6 (7.0)
Male gender, %	75	76	71	77
Atopy, %	26	29	24	24
Continuous smokers, %	34	40	38	40
Continuous ex-smokers, %	46	47	46	46
Smoking pack-yr	44.4 (28.8)	44.3 (31.2)	42.7 (31.2)	45.0 (36.7)
TLCO, mmol/min/kPa	4.95 (2.08)	4.62 (2.04)	5.28 (2.14)	4.38 (2.03)
KCO, mmol/min/kPa/L	1.02 (0.64)	0.98 (0.66)	1.08 (0.50)	0.90 (0.48)
Previous use of regular inhaled corticosteroids, %	52	50	†50	†64
Baseline postbronchodilator FEV_1, L	1.42 (0.47)	1.43 (0.48)	1.47 (0.50)	1.34 (0.47)
Baseline % predicted postbronchodilator FEV_1, L	49.8 (14.9)	51.3 (15.1)	52.0 (14.6)	48.2 (15.4)

*Data are presented as mean (SD) unless otherwise indicated. TLCO = diffusing capacity; KCO = diffusion coefficient.
†$p < 0.01$ between identified groups (Fisher exact test).

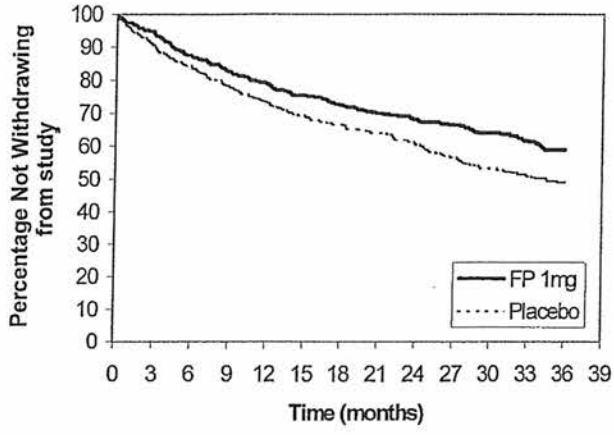

FIGURE 1. Kaplan-Meier plots of the number of patients remaining in the study in both FP and placebo groups, and patient survival allowing for withdrawal from all causes.

defined in the protocol. Thirty-five patients withdrew due to cardiac events, and 30 patients withdrew due to the development of a malignancy. Forty-nine patients either admitted to not taking any study medication or failed to return for follow-up. The remaining patients withdrew due to a variety of other individually infrequent adverse events or for social reasons. There was no difference in the frequency of nonrespiratory withdrawals between the two groups ($p > 0.5$). The time to withdrawal from all causes in placebo- and FP-treated patients is illustrated by the Kaplan-Meier plot in Figure 1. Patients withdrew steadily throughout the study. At all time points, more patients withdrew while receiving placebo at each time point. The median number of exacerbations during FP treatment was 0.99/yr irrespective of subsequent withdrawal. In those receiving placebo, it was 1.05/yr in those completing but 1.69/yr in those who did not complete the trial ($p = < 0.02$).

Spirometry and Withdrawal

The study population was separated into two groups on the basis of an FEV_1 of $< 50\%$ predicted (American Thoracic Society stage 3). In patients with a higher FEV_1, the number of patients completing and withdrawing during the study were similar in patients with a higher FEV_1 ($> 50\%$ predicted), with 46% of the total withdrawing. When the FEV_1 was $< 50\%$ predicted, there was a clear difference between the two treatments, with significantly more patients withdrawing from placebo compared with FP treatment (57% vs 38%, respectively; $p = 0.0002$). The reasons for withdrawal were similar in each group as a percentage of the total causes listed, but the absolute numbers were lower in the FP-treated patients.

The rate of decline in FEV_1 is presented in Figure 2. The effect of treatment on the rate of decline in FEV_1 was the same in patients who withdrew and those who completed the study (Table 2, Fig 2); however, patients who completed the study had a significantly slower decline in FEV_1 than those who withdrew, irrespective of treatment group ($p < 0.02$).

Health Status and Withdrawal

Baseline health status data for the SGRQ and SF-36 were similar in all domains at study entry irrespective of subsequent withdrawal. The rate of decline of health status in those withdrawing in the FP group did not differ from that in the placebo completers (Table 2). In contrast, the deterioration

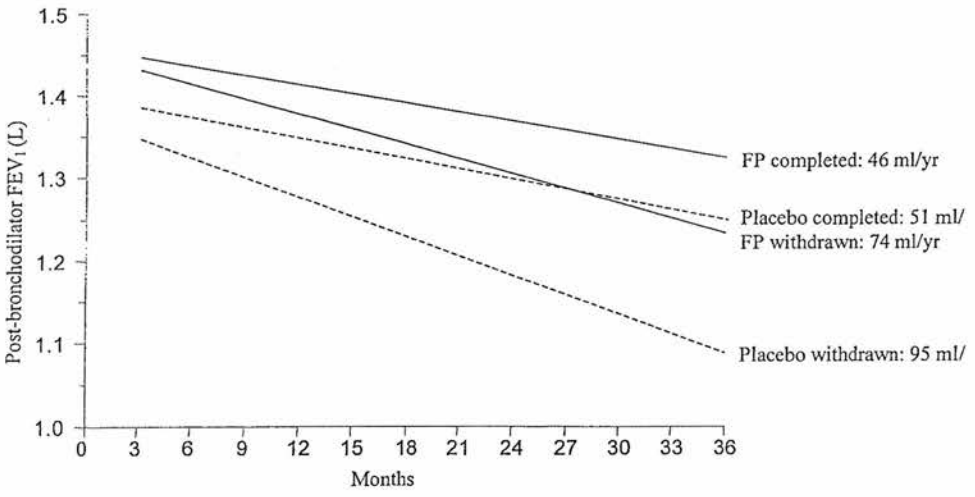

FIGURE 2. Mean rate of change of the postbronchodilator FEV_1 over 3 years in patients receiving placebo who withdrew and completed the study, and those receiving FP who withdrew and completed the study.

Table 2—*Decline in Postbronchodilator FEV_1 and Health Status

Variables	FP			Placebo		
	Completers (n = 211)	Withdrawers (n = 107)	p Value	Completers (n = 175)	Withdrawers (n = 123)	p Value
Postbronchodilator FEV_1	46 mL/yr (n = 220)	74 mL/yr (n = 119)	< 0.02	51 mL/yr (n = 181)	95 mL/yr (n = 144)	< 0.02
SGRQ total	2.00	2.79	0.4	2.65	6.74	0.0001
SGRQ symptoms	1.15	0.64	0.6	1.99	4.81	0.009
SGRQ activity	2.04	3.86	0.08	3.06	7.02	0.0001
SGRQ impacts	2.21	2.80	0.6	2.63	7.35	0.0001
SF-36 physical function	− 1.81	− 2.40	0.6	− 2.82	− 7.10	0.0001
SF-36 physical role	− 3.23	− 3.64	0.9	− 4.47	− 11.06	0.005
SF-36 pain	− 1.25	− 3.55	0.2	− 2.31	− 2.08	0.8
SF-36 health perception	− 2.49	− 2.28	0.9	− 2.25	− 7.10	0.0001
SF-36 energy/vitality	− 1.22	− 2.43	0.3	− 2.07	− 5.59	0.001
SF-36 social function	− 1.22	− 2.43	0.3	− 2.07	− 5.59	0.001
SF-36 mental role	− 4.51	− 6.08	0.6	− 5.40	− 7.82	0.4
SF-36 mental health	− 0.02	− 0.32	0.8	− 0.99	− 2.78	0.06

*Data are presented as U/yr unless otherwise indicated.

in SGRQ total, symptoms, and impacts scores of placebo-treated patients who withdrew was significantly greater than that of placebo completers or the patients treated with FP ($p < 0.01$). The total SGRQ score of patients withdrawing from placebo deteriorated at 6.74 U/yr, equivalent to a clinically noticeable deterioration in health status every 8 months (Fig 3). The rate of change in the SF-36 physical function and health perception scores in placebo-treated patients who withdrew was greater compared to the other three groups ($p < 0.001$).

Discussion

This is the first prospective COPD study in which large numbers of patients failed to complete the intended follow-up period because of nonrandom withdrawal. Like other studies[6–9] of inhaled corticosteroids, our trial did not show a significant effect on the primary outcome measure, rate of decline of FEV_1; however, patients withdrawing from our study had a more rapid deterioration in lung function and health status assessed prior to withdrawal. Loss of these patients from the trial is likely to have reduced the power of the investigation to show differences between groups, and suggests that the effects that were reported are a conservative estimate of the impact of treatment.

At randomization, there were no significant differences between the treatment groups. During the trial, almost half the patients withdrew, principally due to their need for repeated courses of oral

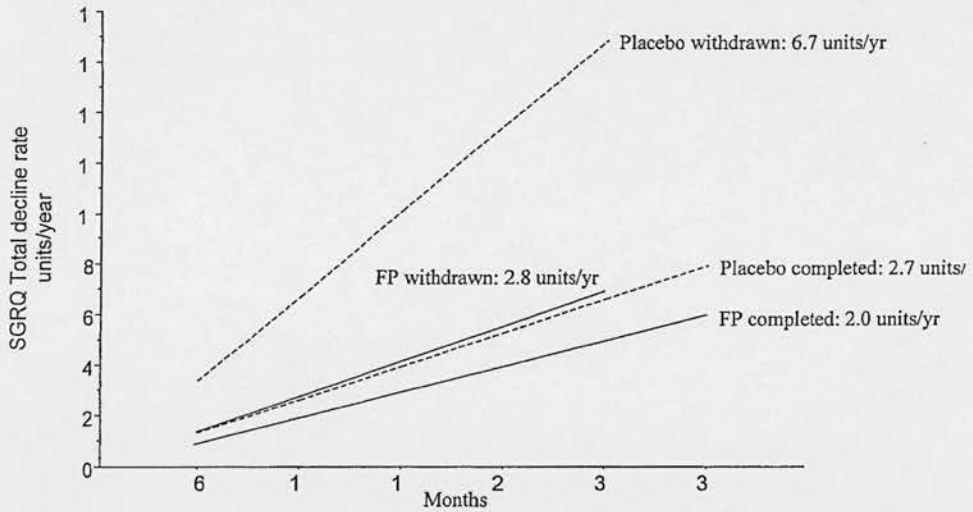

FIGURE 3. Mean rate of change of the SGRQ total score over 3 years in patients receiving placebo who withdrew and completed the study, and those receiving FP who withdrew and completed the study. An increase in score represents worsening of health status.

corticosteroids. This withdrawal due to repeated oral corticosteroid use was more common in placebo-treated patients, and explains the different dropout rates in between the groups. *Post hoc* categorization of patients into completers and withdrawers suggests an explanation for the different dropout rates in the FP- and placebo-treatment groups. Placebo-treated patients who withdrew had a tendency to have a lower initial FEV_1 than those who completed 3 years of follow-up, a finding not seen in FP-treated patients. The effect of the inhaled corticosteroid may have been to allow these more physiologically impaired patients to better cope with exacerbations better, and avoid treatment with oral corticosteroids. Although patients who had previously received inhaled corticosteroids were no different in other respects at study entry,[8] they were more likely to withdraw if randomized to placebo, which is in keeping with other data from the prerandomization phase of this study.[20]

The severity of COPD assessed spirometrically also influenced both the number withdrawing and the number of exacerbations that occurred. Patients with worse spirometric findings were more likely to withdraw and have exacerbations, and this influenced the ability of treatment to show an effect. Thus, the effect of FP treatment on respiratory withdrawals was most evident in patients with more severe disease (American Thoracic Society stage 3, *ie*, $< 50\%$ predicted FEV_1), where 104 patients withdrew due to respiratory causes compared with the 54 patients in the less severely affected groups. These data explain the lower frequency of exacerbations in other trials of inhaled corticosteroids,[6,7] where the baseline FEV_1 was higher. Selection of patients by a specified postbronchodilator FEV_1 is therefore likely to be important when exacerbation frequency is a study outcome. Moreover, the patient who withdrew were those in whom the FEV_1 was declining most rapidly, providing objective confirmation of their greater disease severity.

Health status measurements, whether disease specific or generic, deteriorate in patients with COPD, and this change is less marked in those treated with inhaled corticosteroids.[21] Our analysis shows that an important consequence of effective treatment is to prevent the deterioration in health status in those who would otherwise withdraw. Thus, the health status change of patients receiving FP who withdrew was similar to that in the placebo-treated completers. Impaired health status is associated with increased health-care utilization[22] and increased numbers of exacerbations.[23] The higher median exacerbation frequency in those withdrawing while receiving placebo suggests that exacerbations contribute to their accelerated decline in health status, and the protective effect of FP arises from the lower number of exacerbations observed with this drug.

Differential withdrawal from the study might modify the study outcome. The loss of those patients with the most rapid decline in FEV_1 will reduce the overall power of the study to show a difference. The "healthier survivor" effect seen in the placebo-treated but not the FP-treated patients may reduce the difference between groups in the rate of decline of FEV_1. This may be important because, as others, we used a random effects model to estimate the rate of decline of FEV_1, but this is a conservative approach to detecting differences between treatments, especially if there are differential dropout rates between treatment groups. A theoretical analysis of the magnitude of this effect is shown in Figure 3. Differential dropout rates between treatment groups is a relevant consideration for other potential disease-modifying agents, in which a reduction of exacerbations may also occur and similar problems arise.

Avoiding premature withdrawal is clearly a difficult problem in any study in which an active therapy is compared with a placebo treatment. This is especially so when the treatment is already prescribed by some physicians, and its removal can precipitate an exacerbation.[20] Patients withdrawn should continue to be followed up even if their medication is changed, and future trials should consider less rigorous criteria than those used here to determine when a patient should be discontinued from participating in the study.

Reporting the number of patients leaving a clinical trial provides useful additional information about treatment effectiveness in bronchial asthma,[3,4] and our data suggests that this is also true for COPD. The significantly different outcomes in those withdrawing from active and placebo treatment suggests that an important clinical effect is occurring. Thus, the impact of inhaled corticosteroids in COPD may be rather greater than analyses of individual end points have so far suggested. These benefits are most marked in patients with an $FEV_1 < 50\%$ predicted, and as such are in line with recommendations for treatment suggested in the Global Initiative for Chronic Obstructive Lung Disease management strategy.[13]

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Withdrawal From Treatment as an Outcome in the ISOLDE Study of COPD*

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease

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Background: In chronic obstructive pulmonary disease (COPD), the degree of circadian variation in forced expiratory volume in 1 second (FEV_1) and the influence of anticholinergic blockade is not known. Tiotropium is a long acting inhaled anticholinergic bronchodilator that increases daytime FEV_1 in COPD. We hypothesised that tiotropium would modify the overnight change in FEV_1, and this would be unaffected by the timing of drug administration.

Methods: A double blind, randomised, placebo controlled trial was conducted with tiotropium 18 mg once daily in the morning (09.00 hours), evening (21.00 hours), or an identical placebo. Patients with stable COPD (n = 121, FEV_1 = 41% predicted) underwent spirometric tests every 3 hours for 24 hours at baseline and after 6 weeks of treatment.

Results: There were no significant differences at baseline between the groups. Tiotropium improved mean (SE) FEV_1 (over 24 hours) in the morning (1.11 (0.03) l) and evening (1.06 (0.03) l) groups compared with placebo (0.90 (0.03) l), and nocturnal FEV_1 (mean of 03.00 and 06.00 hours) in the morning (1.03 (0.03) l) and evening (1.04 (0.03) l) groups compared with placebo (0.82 (0.03) l) at the 6 week visit ($p<0.01$). FEV_1 before morning or evening dosing was similar, while the peak FEV_1 moved later in the day with active treatment. The mean percentage change in FEV_1 from 09.00 hours to 03.00 hours (the nocturnal decline in FEV_1) was −2.8% in the morning group, −1.0% in the evening group, and −12.8% in the placebo group. The magnitude of the peak to trough change in FEV_1 was not statistically different.

Conclusions: Tiotropium produced sustained bronchodilation throughout the 24 hour day without necessarily abolishing circadian variation in airway calibre.

Many patients with respiratory disease complain of symptoms which are worse during the night or in the early morning. This has been well documented in bronchial asthma[1 2] but is also reported by patients with chronic obstructive pulmonary disease (COPD).[3–5] In patients with asthma the symptoms have usually been ascribed to a substantial increase in the normal circadian variation in airway calibre,[6] but data in COPD are less convincing and have relied on unsupervised home peak expiratory flow (PEF) recording. Nonetheless, a circadian variation of 16 l/min per day has been reported in COPD and is substantially less than in asthmatic subjects.[7]

There is general agreement that central cholinergic mechanisms are the major determinants of this variation in airway calibre.[8] However, this has been difficult to test in man as the duration of action of existing anticholinergic drugs does not completely span the overnight period.[9] Moreover, the side effects of systemically administered anticholinergic drugs preclude the chronic treatment required to assess this response, as does their attendant sleep disruption. Nonetheless, there are data that suggest that inhaled oxitropium bromide can reduce the overnight fall in PEF in nocturnal asthma.[10]

Tiotropium bromide is a new long acting inhaled anticholinergic bronchodilator that improves lung function for 24 hours after once daily dosing. The pharmacological properties of muscarinic receptor kinetic subselectivity[11 12] and prolonged binding to the M_3 receptor have been proposed as explanations for this prolonged duration of action.[13] An earlier dose ranging study of single dose tiotropium in patients with COPD showed that, despite significant bronchodilation, a nocturnal decline in FEV_1 occurred approximately 15–19 hours after morning inhalation of a single dose.[14] This change was less marked than that with placebo, suggesting that morning administration of tiotropium partially reverses the nocturnal decline in lung function.

Evening administration of tiotropium has not previously been evaluated. The time of administration may influence the pharmacodynamics of some bronchodilators such as theophylline, with evening administration of certain formulations having a more pronounced effect on lung function during the night.[15] Similar time dependent effects of dosing have been seen with corticosteroids in asthma.[16 17]

In this study we examined whether the circadian variation in FEV_1 in patients with COPD was greater than that reported in healthy subjects, whether it could be abolished or reduced by sustained anticholinergic blockade in the airways, and whether the timing of the dose of tiotropium influenced its effect on overnight FEV_1 compared with placebo treated patients.

METHODS

Subjects

All patients recruited were at least 40 years old with a smoking history of at least 10 pack years and a clinical diagnosis and spirometric parameters compatible with COPD as defined by the American Thoracic Society (ATS).[18] Their FEV_1/FVC ratio was less than 70% and their absolute FEV_1 was 25–65% predicted using the European Community for Coal and Steel (ECCS) reference values.[19] Patients with a history of asthma, allergic rhinitis, or atopy, or a total eosinophil count $\geq 600/mm^3$ were excluded, as were those with significant diseases other than COPD. No patient had experienced an exacerbation of COPD within the preceding 4 weeks. Medications not permitted after the run in phase were short acting inhaled anticholinergic drugs, long acting inhaled β agonists, oral β agonists, and theophylline. Use of

other concurrent medication was required to be stable during the study period. The protocol was approved by local institution review boards and informed consent was obtained from all patients.

Study design

A 6 week, multicentre, randomised, double blind, double dummy, parallel group design was used. Three treatment arms were compared: tiotropium 18 μg daily administered at 09.00 hours (Tio-AM), tiotropium 18 μg daily administered at 21.00 hours (Tio-PM), and placebo. All patients inhaled the contents of one capsule twice daily (either placebo or tiotropium, depending on the group). The times of study administration selected were based on the anticipated average time that a person might take morning or evening medication, considering the study design needed to separate the dose-time interval by 12 hours. Study medication was administered by a dry powder device (HandiHaler).

After initial screening, patients entered a 7 day baseline period to ensure clinical stability (no exacerbations). They attended the clinic where spirometric tests were performed 3 hourly over a 24 hour period, at the end of which they received their first morning dose of study medication. They were instructed to take the study medication in the morning (09.00 hours) and evening (21.00 hours) and to record their morning and evening PEF throughout the study in a diary card immediately before administering study medication.

After 6 weeks the patients attended for their second clinic visit. Spirometric assessment began before the administration of the evening dose of medication. Patients remained in the clinic overnight and spirometric tests were again repeated 3 hourly throughout the following day (including overnight measurements and immediately before the morning dose of study medication). Patients were awakened for spirometric testing if necessary.

A continuous 24 ECG (Holter monitor) was recorded during the patients' stay in the clinic at baseline and at 6 weeks. Analysis of the Holter ECG tapes was performed by Hertford Medical BV, Maasdam, The Netherlands by investigators blinded to the purpose of the study. Adverse events were monitored throughout the baseline and 6 week treatment periods.

Study procedures

Baseline spirometric tests were conducted between 08.00 and 12.00 hours. They were conducted in triplicate and met ATS standards of reproducibility.[20] The highest values of FEV_1 and FVC from three reproducible tracings were recorded. Identical portable electronic spirometers (Microlab 3300 Spirometer; Micromedical, Kent, UK) were used for all measurements at all centres. Home PEF recordings were made using a Personal Best Peak Flow Meter (Health Scan Products Inc, Cedar Grove, NJ, USA) and were recorded as the best of three efforts in the morning and the evening.

Data analysis

The primary end point was the mean change from baseline in FEV_1 recorded at 03.00 and 06.00 hours on the morning following the last dose of study medication on visit 4 (after 42 (3) days of treatment). Baseline FEV_1 was derived from the measurements recorded at 03.00 and 06.00 hours before the administration of the study drug on visit 2 (day 1). The overall steady state bronchodilator efficacy of tiotropium was determined by the mean FEV_1 response measured over a 24 hour time interval on visit 4. The mean FEV_1 at baseline was calculated as the mean of the 3 hourly readings measured over 24 hours from 09.00 to 09.00 at visit 2. The mean response was defined as the difference between the mean FEV_1 at baseline (visit 2) and the mean FEV_1 at the end of treatment (visit 4).

The sample size calculation was based on data from previous studies of the effect of tiotropium on FEV_1 in COPD.[14] Assuming a standard deviation of 0.17 l for FEV_1,[21] a sample size of 30 patients per treatment group would be sufficient to detect a difference of 0.15 l in FEV_1 between treatment groups at a 5% level of significance and 90% power using a two tailed *t* test.

Data are presented as mean (SD) for the population and SE for between-group comparisons. Analysis of covariance with terms for treatment and centre and baseline as a covariate was used as the statistical model for all efficacy analyses. The baseline value was included in the analysis of covariance model as a covariate to adjust for any baseline differences between treatment groups. Patients were excluded from individual analysis if adequate data were not available (for example, missing baseline data). Differences were accepted as being statistically significant at $p<0.05$. Circadian variation in peak flow and FEV_1 was calculated as the difference between the highest and lowest values divided by the mean of the values available for that period—that is, all FEV_1 measurements during the 24 hour period and all PEF measurements during the week of study. However, the study was not originally powered to examine circadian variation and the analyses performed for this evaluation were conducted post hoc.

RESULTS

Demographic data

Patient baseline features for the three treatment groups are presented in table 1. The mean age for the groups combined was 65.8 years, 62% were men, and the group mean FEV_1 was 1.08 l (40.8% predicted). The mean smoking history was 44 pack years, with 62% of the total population being ex-smokers. The groups did not differ in their pulmonary function or in their usual pulmonary medication before randomisation (table 1).

Spirometric parameters

Forced expiratory volume in 1 second (FEV_1)

The mean (SE) nocturnal FEV_1 (mean FEV_1 at 03.00 and 06.00 hours) for the Tio-AM, Tio-PM, and placebo groups and the corresponding overall steady state FEV_1 (mean over 24 hours) values are presented in table 2. The differences from placebo in both the morning and evening dosing groups as well as the nocturnal FEV_1 were statistically significant ($p<0.05$) at all time points on day 42. The baseline 24 hour spirometric recordings showed significant circadian variation in FEV_1 in all three patient groups with the highest values recorded at 09.00 hours on the study day and the lowest values occurring at either 03.00 or 06.00 hours on the following morning (fig 1A). The group mean change in FEV_1 between 09.00 and 03.00 hours at baseline was: −180 ml in Tio-AM, −200 ml in Tio-PM, and −120 ml in the placebo group, corresponding to 03.00 hour absolute values of FEV_1 of 0.88, 0.84, and 0.90 l, respectively. The mean FEV_1 over the 24 hour day was 0.96, 0.95 and 0.96 l for the Tio-AM, Tio-PM, and placebo groups, respectively. The mean circadian variation for each group was 33.3%, 35.6% and 25.9%, respectively. There was considerable intersubject variability and these values did not differ statistically between the groups (ANOVA), but in the pairwise comparisons the variation in the Tio-PM group was higher than in the placebo group ($p = 0.03$). However, the baseline variability before treatment was lower in the placebo group and this might influence the results.

When the FEV_1 profile was repeated after treatment, patients receiving placebo had a lower 24 hour mean FEV_1

Table 1 Demographic characteristics of patients at screening (n = 121)

	Tiotropium (pm) (n = 43)	Tiotropium (am) (n = 38)	Placebo (n = 40)	Total (n = 121)
Men (n)	28	21	26	75
Age (years)*	66.1 (6.6)	64.9 (7.7)	66.5 (9.4)	65.8 (7.9)
Duration of COPD (years)*	10.0 (8.5)	12.3 (12.3)	9.9 (7.9)	10.7 (9.7)
Baseline spirometry:*				
FEV_1 (l)	1.09 (0.38)	1.12 (0.45)	1.04 (0.33)	1.08 (0.39)
FEV_1 (% predicted)	41.8 (14.0)	41.9 (13.5)	38.6 (9.6)	40.8 (12.5)
FVC (l)	2.14 (0.67)	2.19 (0.68)	2.15 (0.71)	2.16 (0.68)
FEV_1/FVC (%)	51.8 (11.0)	50.9 (11.0)	49.6 (9.3)	50.8 (10.4)
Total taking pulmonary medication during the baseline period	41 (95.3%)	36 (94.7%)	37 (92.5%)	114
Anticholinergic drugs	15 (34.9%)	14 (36.8%)	18 (45.0%)	47
Beta adrenergics (inhaled)	34 (79.1%)	34 (89.5%)	35 (87.5%)	103
Beta adrenergics (oral)	3 (7.0%)	4 (10.5%)	4 (10.0%)	11
Mucolytic agents	1 (2.3%)	3 (7.9%)	3 (7.5%)	7
Steroid (inhaled)	31 (72.1%)	27 (71.1%)	27 (67.5%)	85
Steroid (oral)	0 (0%)	0 (0 %)	2 (5.0%)	2
Theophylline	2 (4.7%)	1 (2.6%)	2 (5.0%)	5

*Mean (SD).

(0.91 (0.02) l) which was statistically lower than at the baseline visit (0.96 (0.02) l). On this occasion, the peak value occurred at 12.00 hours with the minimum FEV_1 again being recorded between 03.00 and 06.00 hours on the following day, corresponding to an absolute FEV_1 of 0.82 l (fig 1B).

In both tiotropium groups the FEV_1 increased significantly at all time points during the 24 hour observation period compared with placebo (fig 1B). In patients treated with tiotropium the highest FEV_1 now occurred at 12.00 hours, but the nadir remained between 03.00 and 06.00 hours. There was a non-significant trend towards a reduction in the magnitude of overnight decline in FEV_1 compared with placebo when this was expressed as a percentage change from the mean at 09.00 hours (fig 2), but not as an absolute change from the mean daily FEV_1 value (Tio-AM = 60 ml, Tio-PM = 48 ml, placebo = 56 ml).

Individual maximum variation was calculated as the difference between maximum and minimum FEV_1 expressed as a proportional change from the minimum (100 × (maximum − minimum)/minimum). At baseline the mean maximum variation was 41.6%, 46.5%, and 30.2% for Tio-AM, Tio-PM, and placebo, respectively. After treatment the mean maximum variation declined in the Tio-AM (34.5%) and the Tio-PM (37.2%) groups but was similar to baseline in the placebo group (32.7%).

Forced vital capacity

The pattern of nocturnal FVC (mean FVC at 03.00 and 06.00 hours) and overall steady state FVC (mean over 24 hours) was similar to the FEV_1 responses, and both tiotropium groups were statistically better than placebo ($p = 0.0001$). The mean (SE) nocturnal FVC for the Tio-AM, Tio-PM, and placebo groups and the corresponding overall steady state FVC values are presented in table 3. No statistically significant differences were seen between the two tiotropium dosing groups with respect to the nocturnal FVC ($p = 0.61$) and overall steady state FVC ($p = 0.35$). As with FEV_1, the FVC profile after 6 weeks of treatment showed that both tiotropium groups were consistently better than the placebo group throughout the 24 hour observation period.

Peak expiratory flow

The mean morning and evening PEF during the baseline period were comparable across the three treatment groups (table 4). The weekly mean morning and evening PEF for both tiotropium groups was statistically better than for placebo ($p<0.02$, fig 3). For both tiotropium groups the mean weekly morning and evening PEF increased after 1 week on treatment, and remained consistently better than placebo throughout the 6 weeks of treatment.

Adverse events

COPD exacerbations and upper respiratory tract infection were more common with placebo than with Tio-AM and Tio-PM, although the differences were not statistically significant. Exacerbations of COPD and upper respiratory tract infections were diagnosed by the physician and reported as adverse events. Eight patients (20.0%) in the placebo group had a COPD exacerbation compared with four patients

Table 2 Mean* (SE) nocturnal forced expiratory volume in 1 second (FEV_1) and overall steady state FEV_1 differences between treatment groups after 6 weeks of study drug

Treatment	Mean (SE)	Comparison	Difference (SE)	p value	95% CI
Nocturnal FEV_1					
AM	1.03 (0.03)	AM − Placebo	0.21 (0.04)	0.0001	(0.13 to 0.29)
PM	1.04 (0.03)	PM − Placebo	0.21 (0.04)	0.0001	(0.13 to 0.29)
Placebo	0.82 (0.03)	AM − PM	−0.01 (0.04)	0.8529	(−0.09 to 0.07)
Steady state FEV_1					
AM	1.11 (0.03)	AM − Placebo	0.21 (0.04)	0.0001	(0.13 to 0.29)
PM	1.06 (0.03)	PM − Placebo	0.16 (0.04)	0.0001	(0.09 to 0.24)
Placebo	0.90 (0.03)	AM − PM	0.05 (0.04)	0.2127	(−0.03 to 0.12)

*Means are adjusted for centre and baseline.

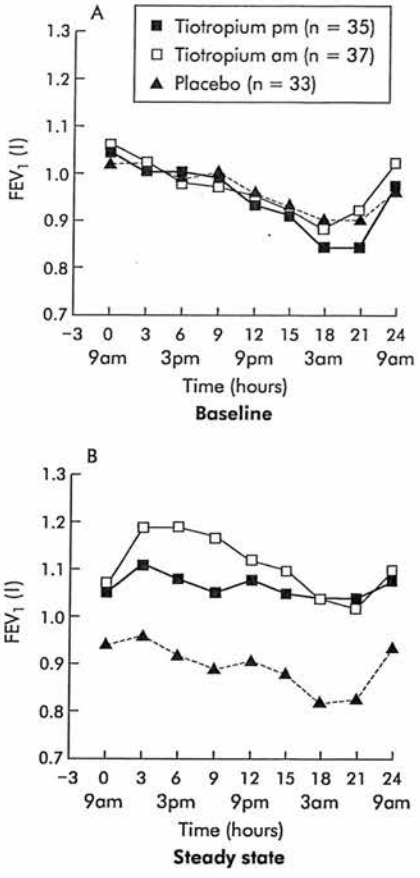

Figure 1 Mean forced expiratory volume in 1 second (FEV_1) in litres over 24 hours (A) at baseline and (B) after 6 weeks (steady state) of tiotropium in the evening (pm), tiotropium in the morning (am), or placebo.

(9.3%) in the Tio-PM group and one (2.6%) in the Tio-AM group. Six patients (15.0%) in the placebo group experienced upper respiratory tract infection compared with three (7.0%) in the Tio-PM group and one (2.6%) in the Tio-AM group. There were no differences in other adverse events in the tiotropium groups compared with the placebo group. Treatment with tiotropium was not associated with cardiac rhythm or heart rate abnormalities as assessed by 24 hour Holter monitoring.

DISCUSSION

Like many other biological variables, airway calibre exhibits a circadian variation during the 24 hour day with maximum values occurring around noon and the minimum values in the early morning.[22] This variability is characteristic of bronchial asthma and is associated with increased levels of inflammatory mediators in the airways during sleep.[16] The practice of defining variability by changes in morning and evening PEF has been transferred to patients with COPD where, contrary to the current definition of "relatively little variation in airflow calibre",[23] several studies have shown evidence of circadian variation.[4 7 24–27] Using the PEF in COPD is potentially misleading as the measurement is effort dependent and underestimates the impairment of FEV_1 in COPD.[19] Previous reports have significant limitations. They included only small numbers of patients and did not obtain measurements during the night.[7 24 26] Some failed to include a control limb when studying bronchodilator effects[24 26] or

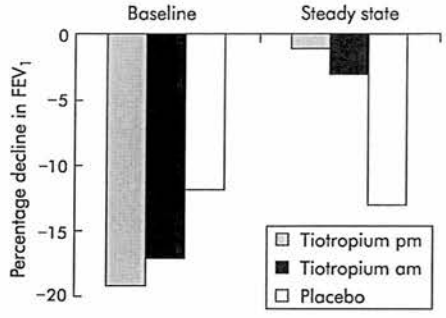

Figure 2 Proportional nocturnal decline in forced expiratory volume in 1 second (FEV_1) at baseline and after 6 weeks of study drug (steady state). Percentage decline in FEV_1 = (FEV_1 9 am − FEV_1 3 am)/FEV_1 9 am × 100.

included patients with substantial degrees of bronchodilator responsiveness.[4] This is the first study to document circadian variation in FEV_1 in patients with stable COPD before and after a long acting inhaled bronchodilator and to include measurements during the early morning hours when FEV_1 is lowest. Our findings have implications both for the mechanisms underlying this process and the interpretation of the results of treatment trials.

Studies of spirometric tests in normal subjects report a mean maximum change across the day of 200 ml in FEV_1.[28] Observations in a large population of healthy individuals whose FEV_1 was measured on different occasions between 09.00 and 21.00 hours confirm that the peak values occurred around midday.[29] They suggested that those who are older, smoke cigarettes, or have some respiratory symptoms show a more marked fall in FEV_1 in the later evening. At baseline in our patients with COPD there was a mean (SE) daily FEV_1 change of 286 (17) ml for the whole group with the maximum value in the late morning and the minimum in the early hours of the morning. This overall pattern was reproducible over the 6 weeks in the placebo group although the 09.00 value tended to be lower, possibly reflecting differences in the duration of effect of other permitted medications. The FVC data parallel those for FEV_1 with no meaningful difference in the FEV_1/FVC ratio throughout the 24 hour day, an observation supportive of consistent effort in performing the measurements throughout the day. The mean PEF was lower in the morning than in the evening throughout the 6 weeks in the placebo treated patients, varying by 13–17 l/min. These values are similar to those in the only other study to report patients of similar severity.[7] These mean data mask significant between-week and between-individual variations and highlight the limitation of using measurements of circadian variation where the precise time of measurement is not known.

Lower respiratory system resistance in COPD rises significantly throughout sleep, independent of sleep stage[30] and, although polysomnographic data were not included in the present study, our data are compatible with this. Increased cholinergic tone in the airway smooth muscle is believed to be a major contributor to this process, but data from the COPD patients treated with tiotropium indicate that this may not be the only factor involved. Tiotropium is an effective inhaled anticholinergic drug which can block methacholine challenge in patients with asthma for long periods.[31] The mean FEV_1 value over the 24 hour day increased after tiotropium and the absolute FEV_1 was always higher at any time point after the active drug than the pretreatment baseline and placebo values. The timing of FEV_1 variation also changed, with the highest FEV_1 occurring between 12.00

Table 3 Mean* (SE) nocturnal forced vital capacity (FVC) and overall steady state FVC differences between treatment groups after 6 weeks of study drug

Treatment	Mean (SE)	Comparison	Difference (SE)	p value	95% CI
Nocturnal FVC					
AM	1.99 (0.05)	AM – Placebo	0.31 (0.07)	0.0001	(0.18 to 0.45)
PM	2.02 (0.05)	PM – Placebo	0.35 (0.07)	0.0001	(0.22 to 0.48)
Placebo	1.68 (0.05)	AM – PM	−0.03 (0.07)	0.6051	(−0.16 to 0.10)
Steady state FVC					
AM	2.12 (0.04)	AM – Placebo	0.32 (0.06)	0.0001	(0.21 to 0.44)
PM	2.07 (0.04)	PM – Placebo	0.27 (0.06)	0.0001	(0.16 to 0.39)
Placebo	1.79 (0.04)	AM – PM	0.05 (0.06)	0.3526	(−0.06 to 0.16)

*Means are adjusted for centre and baseline.

and 18.00 hours, a pattern closer to that described in healthy individuals.[32] Despite this improvement in absolute FEV_1, the difference between the highest and lowest values during the day was similar after the active drug whenever given and resembled that reported in normal subjects.[22] Whether this is due to changes in airway calibre in areas not reached by the inhaler, to different factors modulating airway smooth muscle activation, or simply differences in the control of lung volume or secretion clearance as proposed elsewhere[33] cannot be resolved by our study.

The data illustrate some of the problems in interpreting bronchial reactivity indices in patients with a low baseline FEV_1. If we relate the change in FEV_1 after tiotropium administered at 09.00 hours to a specific time point as in fig 2, reactivity appears to decline even though the absolute change from maximum to minimum is unaffected. Similar problems arise when other indices recommended in population studies are calculated.[34] This emphasises the need to relate such variables to baseline lung function and helps explain the poor concordance between PEF changes and other measures of bronchial reactivity in patients with COPD.[35]

Although the timing of the dose of some drugs, such as corticosteroids in asthma,[16 17] may influence the subsequent FEV_1, this was not seen in these studies with tiotropium in COPD. The absolute change in FEV_1 compared with baseline appeared smaller than that reported in some larger trials,[36] but the changes relative to placebo were similar in magnitude. Nevertheless, the timing of the measurements can influence the end points selected. The 03.00 hours value had a mean difference of 220 ml in the Tio-AM and Tio-PM groups compared with placebo, while the 09.00 hours value had a mean difference of 130 and 110 ml, respectively. This dependence on timing may help explain why patients with COPD vary in response to the same drug in different studies.

In summary, we have found that circadian variations in FEV_1 are present in patients with COPD. This is likely to contribute to the disturbed sleep seen in such patients and reflected in their daytime symptoms. Although the absolute change in FEV_1 over 24 hours is close to normal, it comprises a proportionately greater amount of the waking value and this can complicate the interpretation of the usual measures of bronchial responsiveness. Our findings show that tiotropium once daily, whether administered in the morning or evening, results in sustained improvements in spirometric indices throughout the 24 hours, including improvement in the early morning nadir in spirometric values, without necessarily affecting circadian variability.

Table 4 Mean (SE) baseline weekly means for morning (PEF am) and evening (PEF pm) peak expiratory flow rates (l/min)

	Tiotropium pm (n = 40)	Tiotropium am (n = 37)	Placebo (n = 34)
PEF am	209 (13)	195 (11)	217 (15)
PEF pm	225 (12)	205 (11)	223 (15)

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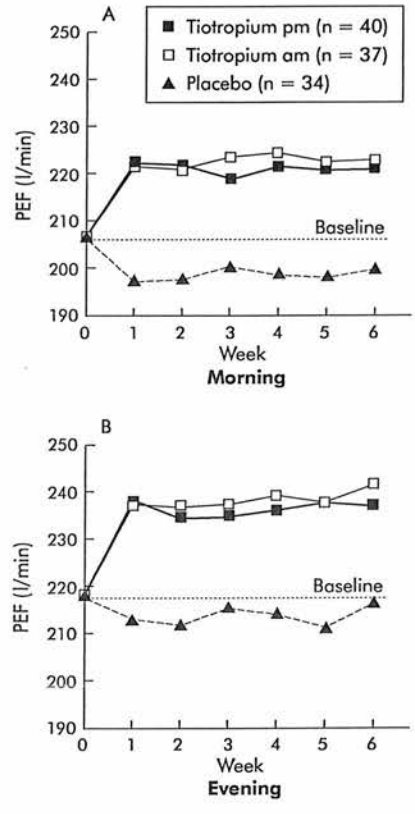

Figure 3 The mean of the weekly means for (A) morning and (B) evening PEF (l/min) over 6 weeks of treatment with either tiotropium in the evening (pm), tiotropium in the morning (am), or placebo.

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PMAC contributed patients to the study,helped develop the data analysis plan and wrote the manuscript together with SK. JvN contributed patients, LT organised the study implementation and AL undertook the statistical analysis. All authors contributed to development of the study protocol, data interpretation, and to the final manuscript.

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Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease

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Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial

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Abstract

Objectives To determine the effect of long term inhaled corticosteroids on lung function, exacerbations, and health status in patients with moderate to severe chronic obstructive pulmonary disease.

Design Double blind, placebo controlled study.

Setting Eighteen UK hospitals.

Participants 751 men and women aged between 40 and 75 years with mean forced expiratory volume in one second (FEV_1) 50% of predicted normal.

Interventions Inhaled fluticasone propionate 500 μg twice daily from a metered dose inhaler or identical placebo.

Main outcome measures Efficacy measures: rate of decline in FEV_1 after the bronchodilator and in health status, frequency of exacerbations, respiratory withdrawals. Safety measures: morning serum cortisol concentration, incidence of adverse events.

Results There was no significant difference in the annual rate of decline in FEV_1 ($P = 0.16$). Mean FEV_1 after bronchodilator remained significantly higher throughout the study with fluticasone propionate compared with placebo ($P < 0.001$). Median exacerbation rate was reduced by 25% from 1.32 a year on placebo to 0.99 a year on with fluticasone propionate ($P = 0.026$). Health status deteriorated by 3.2 units a year on placebo and 2.0 units a year on fluticasone propionate ($P = 0.0043$). Withdrawals because of respiratory disease not related to malignancy were higher in the placebo group (25% *v* 19%, $P = 0.034$).

Conclusions Fluticasone propionate 500 μg twice daily did not affect the rate of decline in FEV_1 but did produce a small increase in FEV_1. Patients on fluticasone propionate had fewer exacerbations and a slower decline in health status. These improvements in clinical outcomes support the use of this treatment in patients with moderate to severe chronic obstructive pulmonary disease.

Introduction

Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide,[1,2] and its prevalence is rising.[3] It occurs predominantly in tobacco smokers and is characterised by an increase in the annual rate of decline of forced expiratory volume in one second (FEV_1).[4] As lung function deteriorates, substantial changes in general health occur.[5] Smoking cessation reduces the rate of decline in FEV_1 in people with this disease,[6] but no pharmacological intervention has been shown to modify the progression of disease or the associated decline in health status.

In at least 10% of patients with stable chronic obstructive pulmonary disease FEV_1 will increase significantly after oral prednisolone.[7] A large, retrospective, open study reported a reduction in the rate of decline of FEV_1 in those taking oral corticosteroids.[8] Recently, two studies over three years of inhaled budesonide 800 μg in mild to moderate chronic obstructive pulmonary disease found no effect of treatment on the rate of decline in FEV_1.[9,10] Clinical outcomes such as exacerbations, however, were infrequent and health status either showed no benefit of budesonide[9] or was not assessed.[10]

The inhaled steroids in obstructive lung disease in Europe (ISOLDE) study was designed to test the effect of inhaled fluticasone propionate 500 μg twice daily on the rate of decline of FEV_1 and other relevant clinical outcomes.

Participants and methods

Participants

Eighteen UK hospitals participated. Patients were current or former smokers aged 40-75 years with non-asthmatic chronic obstructive pulmonary disease. Baseline FEV_1 after bronchodilator was at least 0.8 litres but less than 85% of predicted normal, and the ratio of FEV_1 to forced vital capacity was less than 70%. Previous use of inhaled and oral corticosteroids was permitted. Patients were excluded if their FEV_1 response to 400 μg salbutamol exceeded 10% of predicted normal, they had a life expectancy of less than five years from concurrent diseases, or they used β blockers. Nasal and ophthalmic corticosteroids, theophyllines, and all other bronchodilators were allowed during the study.

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The protocol was approved by each centre's local ethical committee and patients provided written informed consent.

Trial design

Patients were recruited between 1 October 1992 and 31 March 1995. Eligible patients entered an eight week run-in period after withdrawal from any oral or inhaled corticosteroids. After clinic visits at 0, 4, and 8 weeks (visits 0, 1, and 2, respectively) patients were randomised to receive either fluticasone propionate 500 μg or an identical placebo twice daily administered from a metered dose inhaler and with a spacer device by using 10 tidal breaths after each of two actuations. We used a computer generated allocation schedule stratified by centre (block size of six). Patients were randomised sequentially from a list comprising treatment numbers only. Throughout the trial patients used salbutamol (100 μg/puff) or ipratropium bromide (40 μg/puff), or both, for symptomatic relief.

Before the double blind phase, and if not contraindicated, patients received oral prednisolone 0.6 mg/kg/day for 14 days, after which spirometry was performed. These data were used to test whether the acute corticosteroid response could predict those patients who would benefit from long term inhaled corticosteroids. During the three year double blind phase, participants visited a clinic every three months for spirometry, recording of exacerbations, and safety assessments.

The primary end point was the decline (ml/year) in FEV_1 after bronchodilator. About 450 patients with two or more measurements of FEV_1 during treatment were required to detect a treatment difference of 20 ml/year, assuming a linear decline and a SD of 75 ml/year, with 80% power. Other key end points were frequency of exacerbation, changes in health status, withdrawals because of respiratory disease, morning serum cortisol concentrations, and adverse events.

Measurements

Spirometry measurements were recorded by well trained staff using a standardised procedure on new Sensormedics 2130D spirometers. Quality control included a computer generated check against the ATS criteria[11] and a central manual check for acceptability and reproducibility for all measurements, resulting in standards comparable with the lung health study.[12] Visits were rescheduled to four weeks after any respiratory infections or exacerbations of the disease.

An exacerbation was defined as worsening of respiratory symptoms that required treatment with oral

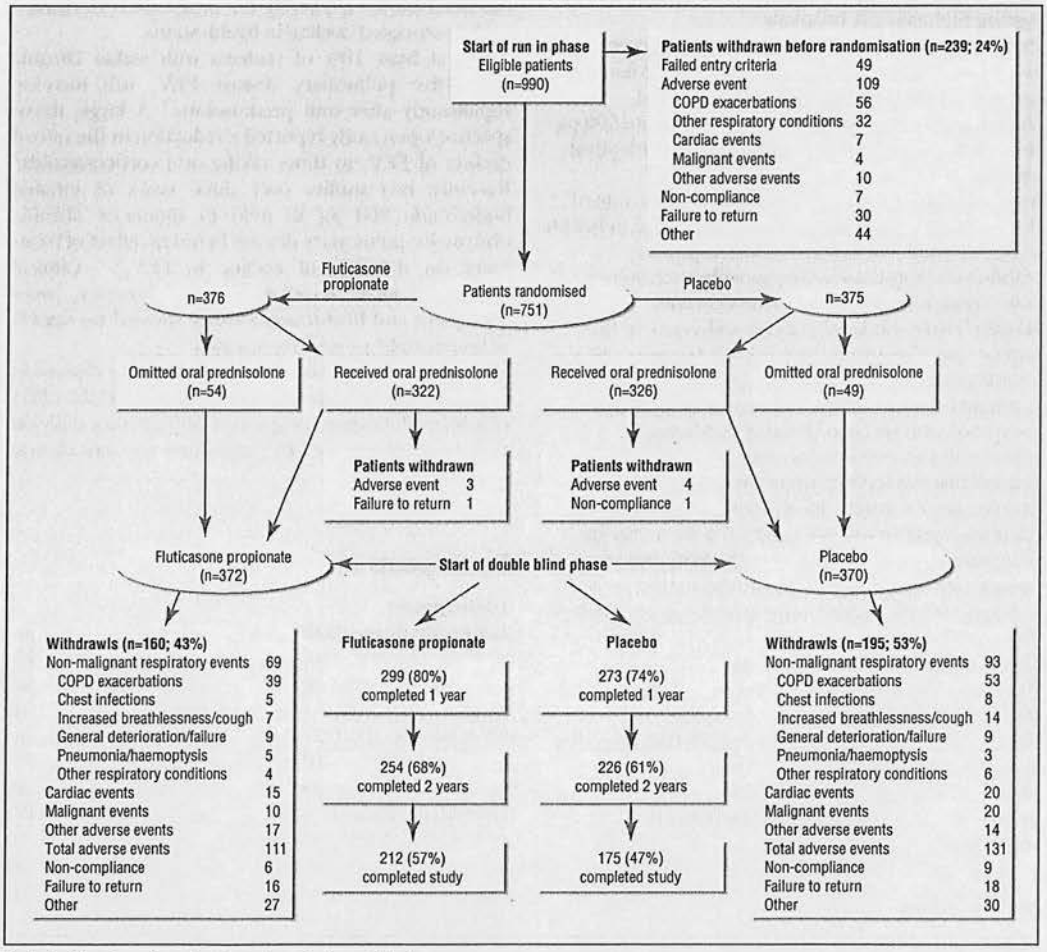

Fig 1 Profile of number of patients at each phase of study

corticosteroids or antibiotics, or both, as judged by the general practitioner; specific symptom criteria were not used. Patients were withdrawn from the study if the number of exacerbations that required corticosteroids exceeded two in any three month period.

Health status was assessed at baseline and six monthly thereafter by using the disease specific St George's respiratory questionnaire (SGRQ).[13] This questionnaire is sensitive to changes in treatment.[14] A change in total score of four or more units represents a clinically important change in the patient's condition.[5] Serum cortisol concentrations were measured before randomisation (baseline) and every six months during treatment. Samples were taken between 8 am and 10 am and were analysed with the ELISA-Boehringer Mannheim ES700 method.

At each visit patients were questioned about smoking status. Non-smoking was checked with exhaled carbon monoxide and urinary cotinine measurements. Self declared non-smokers were classified as smokers if cotinine was >40 ng/ml or carbon monoxide was >10 ppm at two visits. For analysis patients were categorised as continuous smokers, continuous former smokers, or intermittent smokers during the study.

Statistical analysis

Analyses for each parameter included all randomised patients with at least one valid measurement. To use all patient data we adopted the mixed models approach[15] for the primary analysis of FEV_1 and total score. This is the most suitable technique for estimating rates of change, with allowance for the correlation structure of repeated measures data. Regression estimates were adjusted for patient differences in the number of observations contributing to the model and for variances within patients.[16] Fixed effects were time and five covariates: baseline value centre, age, sex, and smoking status. Baseline FEV_1 was the mean at four and eight weeks of the run-in period—that is, at least four weeks after withdrawal of corticosteroids. Subject effects were assumed to be random. The treatment by time interaction tested for a differential treatment effect on the rate of change in FEV_1 or respiratory questionnaire score. The model for FEV_1 also included a treatment main effect to help to account for the early non-linear treatment changes. Measurements at the end of the prednisolone trial were excluded from the model of decline in FEV_1. FEV_1 was also compared by using analysis of covariance after 3, 6, 12, 24, and 36 months to investigate treatment differences over time.

Patient exacerbation rates were calculated as the exacerbation number per treatment days and extrapolated-interpolated to a number per treatment year. The Wilcoxon rank sum test,[17] stratified by centre-,tested for treatment differences.

Fisher's exact test compared treatment withdrawals due to respiratory causes. These included any non-malignant lower respiratory diseases. Analysis of covariance compared data on log transformed serum cortisol concentration during treatment, adjusted for baseline. Tests were two sided, with a 5% significance level.

Results

Patient demographics

Of the 751 patients randomised, 376 received fluticasone propionate and 375 placebo (figure 1). During the double blind phase, 160 patients (43%) withdrew from the fluticasone propionate group and 195 patients (53%) from the placebo group, the commonest reason being frequent exacerbations of chronic obstructive pulmonary disease. Mean FEV_1 at visit two was 160 ml lower in patients who withdrew from placebo compared with those who did not withdraw (1.30 litre *v* 1.46 litre); patients who withdrew from fluticasone propionate had a 40 ml higher FEV_1 compared with those who did not withdraw (1.44 litre *v* 1.40 litre). Treatment groups were well matched at baseline (table 1).

Changes in FEV_1

There was a fall in mean FEV_1 after bronchodilator during the the run-in (placebo 75 ml, fluticasone propionate 65 ml) (fig 2). The effect was greater in patients who withdrew from inhaled corticosteroids at run-in (89 ml compared with 47 ml in the steroid naive group). After oral prednisolone there was a 60 ml (SD 170 ml) improvement in mean FEV_1 after bronchodilator in both treatment groups. Subsequently mean FEV_1 declined gradually in the fluticasone propionate group whereas in the placebo group it fell within three months to values before prednisolone treatment.

The annual rate of decline in FEV_1 was 59 ml/year in the placebo group and 50 ml/year in the fluticasone propionate group ($P = 0.16$) (table 2). This small difference in slopes was uninfluenced by smoking status, age, sex, or FEV_1 response to the oral corticosteroid trial. The predicted mean FEV_1 at three and 36 months in

Table 1 Baseline characteristics of randomised population. Figures are means (SD) unless stated otherwise

	Placebo	Fluticasone propionate
No of patients randomised	375	376
Age (years)	63.8 (7.1)	63.7 (7.1)
Women	97	94
Body mass index (kg/m^2)	24.9 (4.7)	24.5 (4.8)
Evidence of atopy*	91	103
Smoked throughout trial	147	137
Former smoker throughout trial	172	176
Smoking pack years at randomisation†	44 (34)	44 (30)
Previous use of regular inhaled corticosteroids	214	192
Lung function at visit 0‡:		
After salbutamol (400 μg) FEV_1	1.40 (0.48)	1.42 (0.47)
As % predicted normal	50.0% (14.9%)	50.3% (14.9%)
Change in FEV_1 after salbutamol (400 μg)	0.13 (0.10)	0.13 (0.10)
As % predicted normal	4.4% (3.4%)	4.4% (3.5%)
After salbutamol (400 μg) FVC	3.29 (0.80)	3.37 (0.82)
After salbutamol (400 μg) FEV_1:FVC	43.0% (11.0%)	43.0% (12.0%)
Baseline (average of visit 1 and 2)§:		
FEV_1 before bronchodilator	1.23 (0.47)	1.25 (0.44)
FEV_1 after bronchodilator (salbutamol 400 μg and ipratropium bromide 80 μg)	1.40 (0.49)	1.42 (0.47)
Respiratory questionnaire total score¶	49.9 (17.4)	47.7 (17.6)

FEV_1=forced expiratory volume in one second in litres; FVC=forced vital capacity.
*Atopy was defined as being positive response to skin prick testing with common inhalant allergens. Missing data—placebo: 14; fluticasone propionate: 20.
†Missing data—placebo: 37; fluticasone propionate: 16.
‡Missing data—placebo: 4; fluticasone propionate: 3.
§Missing data—placebo: 1; fluticasone propionate: 0.
¶Score of zero indicates no health impairment and 100 represents worst possible score. Missing data—placebo: 8; fluticasone propionate: 7.

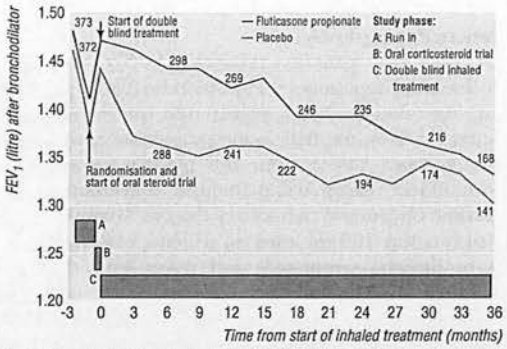

Fig 2 Mean FEV_1 (litres) after bronchodilator by time from start of double blind treatment. Numbers reflect patients with valid readings at each time point. Measurements within four weeks of exacerbation are excluded. Direct comparisons of FEV_1 means at each time point are not possible because fewer patients remained in the study as it progressed

the fluticasone propionate group was 76 ml and 100 ml higher, respectively, than in the placebo group (mixed effects model $P<0.001$). The analysis of covariance showed that FEV_1 in the fluticasone propionate group was higher than in the placebo group by at least 70 ml at each time point ($P\leq0.001$). There was no significant relation between FEV_1 response to oral corticosteroid or fluticasone propionate ($P=0.056$).

Exacerbations

The median yearly exacerbation rate was lower in the fluticasone propionate group (0.99 per year) compared with the placebo group (1.32 per year), a reduction of 25% in those receiving fluticasone propionate ($P=0.026$).

Health status

At baseline the total respiratory questionnaire score was not significantly different between treatment groups (table 1), and it did not change significantly over the first six months of treatment (placebo: up 1.2 (SD 11.9); fluticasone propionate: down 0.5 (SD11.8); $P=0.09$). Thereafter it increased (that is, health status declined) over time (figs 3 and 4). This increase was linear ($P<0.0001$). The respiratory questionnaire score worsened at a faster rate ($P=0.004$) with placebo (3.2 units/year) than with fluticasone propionate (2.0 units/year).

Withdrawals

More patients in the placebo group than in the fluticasone propionate group withdrew because of respiratory disease that was not associated with malignancy (25% *v* 19%, respectively; $P=0.034$).

Safety

Reported events were similar between treatments (table 3), except for a slightly higher incidence of events related to inhaled glucocorticoid in the fluticasone propionate group.

There was a significant ($P\leq0.032$) yet small decrease in mean cortisol concentrations with fluticasone propionate compared with placebo (table 4). No more than 5% of patients on fluticasone propionate had values below the normal range during the study at any time. No decreases were associated with any signs or symptoms of hypoadrenalism or other clinical effects.

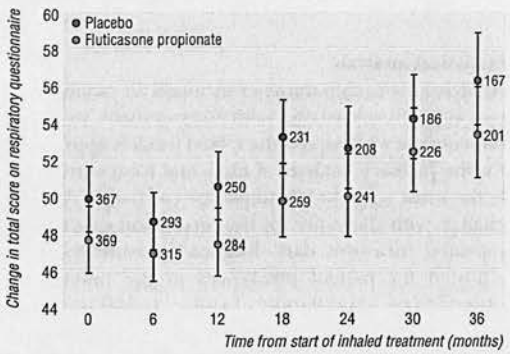

Fig 3 Effect of treatment on decline in health indicated by increasing total scores on respiratory questionnaire (means (95% confidence intervals) calculated from analyses of covariance). Numbers at each assessment indicate number of patients for whom measurements of health status were available at that visit. Direct comparisons of respiratory questionnaire scores at each time point are not possible because fewer patients remained in the study as it progressed

Table 2 Results from efficacy analyses. Mixed effects model analyses adjusted for covariates and Wilcoxon Mann-Whitney test adjusted for centre

Efficacy parameter	Placebo	Fluticasone propionate	Treatment difference between drug and placebo (95% CI)	P value
FEV_1 after bronchodilator:				
No of patients	325*	339*		
Mean change in FEV_1 ml/year (SE)	−59 (4.4)	−50 (4.1)	9 (6.0) (−3 to 20)	0.161
Predicted FEV_1 at 3 months	1.37	1.44	0.076 (0.056 to 0.097)	<0.001
Predicted FEV_1 at 3 years	1.20	1.30	0.100 (0.064 to 0.135)	<0.001
Health status:				
No of patients	291*	309*		
Mean change in questionnaire score (SE) (units/year)	3.17 (0.31)	2.00 (0.29)	−1.17 (0.40) (−1.95 to −0.39)	0.004
Annual exacerbation rate:				
No of patients	370	372		
Mean (SD) rates	1.90 (2.63)	1.43 (1.93)		
Median (range) rates	1.32 (0 to 30)	0.99 (0 to 26)	−0.3 (−0.4 to 0.0)†	0.026

FEV_1=forced expiratory volume in one second in litres.
*Numbers are smaller than randomised population for FEV_1 and health status because of patient withdrawals, missing assessments, or respiratory infections or exacerbations (affects FEV_1 only).
†Zero values are possible in 95% confidence intervals with non-parametric analyses that show P values ≤0.05 because method of calculation of confidence intervals differs from non-parametric test.

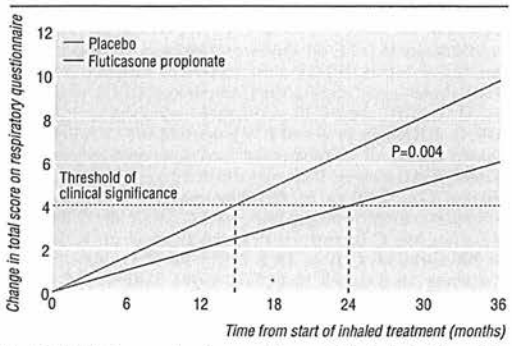

Fig 4 Weighted regressions from random coefficients (mixed) model (see text) to account for the effect of differences in the number of observations between patients, with adjustment for baseline covariates (baseline questionnaire score, age at entry, sex, centre, and smoking during the study)

Table 3 Number of patients with each category of adverse events during double blind period

	Placebo (n=370)	Fluticasone propionate (n=372)
Serious adverse events:		
Any event	148	141
Lower respiratory	101	87
Cardiovascular	44	40
Gastrointestinal	13	19
Deaths:		
Total	36	32
Non-malignant respiratory	6	9
Cardiovascular	12	10
Cancers	14	8
Other	4	5
Inhaled glucocorticoid-related events:		
Hoarseness/dysphonia	16	35
Throat irritation	27	43
Candidiasis of mouth/throat	24	41
Events possibly attributed to systemic absorption:		
Bruising*	15	27
Fractures	17	9
Cataracts	7	5

*Includes ecchymotic rash (1 placebo patient, 8 fluticasone propionate patients).

Discussion

Inhaled corticosteroids have been used widely in the United Kingdom for the empirical treatment of symptomatic chronic obstructive pulmonary disease, but evidence to support this practice is limited. Unlike early reports,[18 19] our study in moderate to severe chronic obstructive pulmonary disease found no effect of corticosteroids on the rate of decline in FEV_1—a finding consistent with two recent budesonide studies in mild disease.[9 10] Like Euroscop, a study in continued smokers,[10] we found a small improvement in FEV_1 after bronchodilator at three months, which was maintained throughout the study. The clinical significance of this change in airway function is unclear. Our study also showed no significant relation between corticosteroid trial response and response to long term inhaled corticosteroid.

The exacerbation rate for placebo was similar to that seen in previous reports,[20] but for fluticasone propionate it was 25% lower. Precise definition of an exacerbation is difficult in ambulant patients with chronic obstructive pulmonary disease, but, by using the operational approach adopted in ISOLDE, reductions in exacerbation severity were seen in another study of patients with moderately severe disease treated for six months with fluticasone propionate.[21] During the ISOLDE run-in we also observed that withdrawal of inhaled corticosteroids was associated with an increased likelihood of an exacerbation.[22] These observations suggest that inhaled corticosteroids do modify the risk of symptomatic deterioration in chronic obstructive pulmonary disease.

Assessment of of health status is recognised as an important additional measurement in patients with chronic respiratory disease and is a better predictor of admission to hospital and death within 12 months than FEV_1.[23] The baseline respiratory questionnaire score showed significant impairment, in keeping with other populations with similar reductions in FEV_1.[13 14] This study shows for the first time that, like FEV_1, health status declines at a measurable rate in patients with moderate to severe chronic obstructive pulmonary disease. Fluticasone propionate significantly reduced this rate of decline, delaying the average time for a clinically important reduction in health status from 15 to 24 months. As the respiratory questionnaire has only a weak correlation with FEV_1,[5] it must be reflecting other disease components other than airflow limitation.

Limitations

Several factors, including disease severity, comorbidity, and study duration, contributed to the high withdrawal rate. Patients were also actively withdrawn from the study and not subsequently followed up if they experi-

Table 4 Morning serum cortisol concentration (nmol/l) for patients who provided valid data (8 am to 10 am samples only) during double blind period

	Placebo (n=370)			Fluticasone propionate (n=372)		
Time point	Patients with valid samples	Geometric mean* serum cortisol (CV†)	No (%) of patients with values below normal range (150-700 nmol/l)	Patients with valid samples	Geometric mean serum cortisol * (CV†)	No (%) of patients with values below normal range (150-700 nmol/l)
Baseline	265	344 (33)	5 (2)	265	353 (31)	4 (2)
6 months	260	345 (33)	3 (1)	272	311 (42)	2 (1)
12 months	209	352 (34)	3 (1)	238	316 (45)	13 (5)
24 months	136	345 (34)	1 (1)	160	303 (44)	5 (3)
36 months	93	354 (33)	1 (1)	96	310 (35)	4 (4)
>1 point during double blind treatment	299	—	4 (1)	331	—	17 (5)

*Least squares means from analysis of covariance of log transformed serum cortisol concentrations were back transformed to give geometric means.
†CV=coefficient of variation (%).

What is already known on this topic

Inhaled corticosteroids are widely prescribed for patients with chronic obstructive pulmonary disease, although there are few studies to support this

A meta-analysis of three small studies showed improvements in FEV_1 with high dose beclomethasone dipropionate or budesonide but no benefit from medium dose treatment

In two recent large studies, budesonide in medium dose produced either no benefit or a small initial improvement in FEV_1

What this study adds

This study measured progressive decline in health status of patients with chronic obstructive pulmonary disease rather than just the FEV_1

In patients with moderate to severe disease, fluticasone propionate 1 mg daily resulted in fewer exacerbations, a reduced rate of decline in health status, and higher FEV_1 values than placebo treatment

Serious side effects were similar to placebo, topical side effects were increased

These data provide a rationale for the use of high dose inhaled corticosteroids in patients with moderate to severe chronic obstructive pulmonary disease

enced frequent exacerbations; this is an acknowledged limitation of the study. The effect of the differential rate of withdrawal from treatment is difficult to quantify, nevertheless it is likely to have led to a conservative estimate of benefit with fluticasone propionate.

Reports of adverse events for each treatment were generally similar, although the incidence of events related to glucocorticoids was slightly higher in the fluticasone propionate group. The incidence of fractures was low (2%) and similar to that reported in Euroscop.[10] No more than 5% of patients on fluticasone propionate had cortisol concentrations below the normal range at any time during treatment. Similar reassuring data have been reported from a two year placebo controlled study of fluticasone propionate 500 μg twice daily in adults with mild asthma.[24]

Conclusions

We found no benefit of fluticasone propionate on the rate of decline in FEV_1, although small improvements in FEV_1 were seen. Unlike the two studies in patients with milder disease, where other clinical outcomes were less measurable,[9 10] we found that fluticasone propionate 500 μg twice daily significantly reduced exacerbations and the rate of decline in health status. These data provide a rationale for the current practice of using use of inhaled corticosteroids at this dose in patients with moderate to severe chronic obstructive pulmonary disease.

Dr G F A Benfield, Dr M D L Morgan, Dr J C Pounsford, Dr R M Rudd, and Professor S G Spiro provided input into the design of the study. The scientific committee members comprised: Dr G F A Benfield, Professor P M A Calverley, Dr J Daniels, Dr A Greening, Professor G J Gibson, Professor P W Jones, Dr M D L Morgan, Dr R Prescott, Dr J C Pounsford, Dr R M Rudd, Professor D Shale, Professor S G Spiro, Mrs J Waterhouse, Dr J A Wedzicha, and Dr D Weir. The steering committee members were Mrs G Bale, Dr P S Burge, Professor P W Jones, and Dr G F A Benfield. Quality control of spirometry data was supervised by Jonathon Daniels and Geraldine Bale, who also acted as study nurse coordinator. Contributions in recruiting patients and with data collection were provided by Professor J G Ayres, Mrs G Bale, Dr N Barnes, Mrs C Baveystock, Dr G F A Benfield, Ms K Bentley, Dr Birenacki, Ms G Boar, Dr P Bright, Ms M Campbell, Ms P Carpenter, Ms S Cattell, Dr I I Coutts, Dr L Davies, Ms C Dawe, Ms J Dowselt, Ms K Dwyer, Mrs C Evans, Ms N Fasey, Dr A G Fennerty, Dr D Fishwick, Ms H Francis, Dr T Frank, Mrs D Frost, Professor G J Gibson, Dr J Hadcroft, Dr M G Halpin, Mrs O Harvey, Dr P Howard, Dr N A Jarad, Ms J Jones, Dr K Lewis, Mrs F Marsh, Mrs N Martin, Dr M D L Morgan, Ms L Morgan, Mrs W McDonald, Ms T Melody, Dr R D H Monie, Dr M F Muers, Dr R Niven, Dr C O'Brien, Ms V O'Dwyer, Ms S Parker, Dr M Peake, Dr W H Perks, Professor C A C Pickering, Dr J C Pounsford, Mrs K Pye, Mr G Rees, Ms A Reid, Ms K Roberts, Mrs C Robertson, Dr R M Rudd, Ms S Rudkin, Mr S Scholey, Dr P Scott, Dr T Seemungal, Ms S Shaldon, Dr C D Sheldon, Ms T Small, Professor S G Spiro, Dr J R Stradling, Ms H Talbot, Mrs J Waterhouse, Mrs L Webber, Dr J A Wedzicha, and Ms M J Wild.

Contributors: PSB and PMAC had the original idea for the present study, helped with the study design, recruited large numbers of patients, advised on data analysis, and helped with the writing of the paper. PSB chaired the scientific committee responsible for coordinating analyses, publications, and substudies. He is also the guarantor of the paper. PMAC chaired the steering committee that facilitated and monitored study progress. PWJ advised on collection and analyses of health status questionnaire data, recruited patients into the study, and helped with the writing of the paper. SS advised on data collection and carried out the health status analyses. JAA analysed the clinical efficacy data. TKM managed data collection and helped with data interpretation and the writing of the paper.

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Competing interests: PSB has received financial support for research and attending meetings and has received fees for speaking and consulting. He also has shares in GlaxoWellcome. PMAC has received grant support and has spoken at several meetings financially supported by GlaxoWellcome. PWJ has received funds for research and members of staff from GlaxoWellcome. SS has received funds for research and members of staff from GlaxoWellcome. JAA and TKM are both employed by GlaxoWellcome. Fluticasone propionate is manufactured by Allen and Hanburys, which is owned by GlaxoWellcome.

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Comparing health inequality in men and women: prospective study of mortality 1986-96

Amanda Sacker, David Firth, Ray Fitzpatrick, Kevin Lynch, Mel Bartley

Abstract

Objectives To study prospectively the differences in health inequality in men and women from 1986-96 using the Office for National Statistics' longitudinal study and new socioeconomic classification. To assess the relative importance of social class (based on employment characteristics) and social position according to the general social advantage of the household to mortality risk in men and women.
Design Prospective study.
Setting England and Wales.
Subjects Men and women of working age at the time of the 1981 census, with a recorded occupation.
Main outcome measures Mortality.
Results In men, social class based on employment relations, measured according to the Office for National Statistics' socioeconomic classification, was the most important influence on mortality. In women, social class based on individual employment relations and conditions showed only a weak gradient. Large differences in risk of mortality in women were found, however, when social position was measured according to the general social advantage in the household.
Conclusions Comparisons of the extent of health inequality in men and women are affected by the measures of social inequality used. For women, even those in paid work, classifications based on characteristics of the employment situation may give a considerable underestimate. The Office for National Statistics' new measure of socioeconomic position is useful for assessing health inequality in men, but in women a more important predictor of mortality is inequality in general social advantage of the household.

Introduction

Social variation in morbidity and mortality in women whose social position is measured according to their own occupation is often found to be less than that of men.[1-4] The extent of social inequality in women's health is known to be particularly sensitive to the way in which inequality is defined and measured.[1 5 6] When women's social position is classified according to the occupation of their male partners, male and female health gradients are more similar.[7 8] In estimates of health inequality there is comparatively little discussion of these apparent sex differences.

It is now possible to study sex differences in health inequality with distinct validated measures of social position and advantage, one based on relations and conditions of employment and the other on material cultural aspects of lifestyle outside the workplace. The Office for National Statistics (ONS) has recently adopted a new measure of social inequality: the ONS socioeconomic classification, for use in the 2001 census and official surveys.[9] This measure allocates occupations to social classes on the basis of aspects of the work situation, in particular the extent to which members of an occupation have control over their own work and that of others.

The other measure is the Cambridge scale, which is based on general social and material advantage and lifestyle as reflected in choices of friendship.[10-12] Both measures are being increasingly used in health studies and have been found to be related to mortality, morbidity, and health related behaviour.[13-18]

We aimed to determine whether social gradients in mortality in women in England and Wales during 1986-96 were less noticeable than in men, and whether this depended on the measure of social inequality used.

Subjects and methods

Sample

The ONS longitudinal study is an approximate 1% sample of the population of England and Wales. Sampling was begun at the time of the 1971 census when all those born on any one of four days in the year were entered into the dataset. The study is regularly updated to include new members born on any one of the four designated dates.[19] Vital events including mortality are

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continued over

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@ Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial

*Peter Calverley, Romain Pauwels, Jørgen Vestbo, Paul Jones, Neil Pride, Amund Gulsvik, Julie Anderson, Claire Maden for the TRISTAN (TRial of Inhaled STeroids ANd long-acting β_2 agonists) study group**

Summary

Background Inhaled longacting β_2 agonists improve lung function and health status in symptomatic chronic obstructive pulmonary disease (COPD), whereas inhaled corticosteroids reduce the frequency of acute episodes of symptom exacerbation and delay deterioration in health status. We postulated that a combination of these treatments would be better than each component used alone.

Methods 1465 patients with COPD were recruited from outpatient departments in 25 countries. They were treated in a randomised, double-blind, parallel-group, placebo-controlled study with either 50 µg salmeterol twice daily (n=372), 500 µg fluticasone twice daily (n=374), 50 µg salmeterol and 500 µg fluticasone twice daily (n=358), or placebo (n=361) for 12 months. The primary outcome was the pretreatment forced expiratory volume in 1 s (FEV_1) after 12 months treatment' and after patients had abstained from all bronchodilators for at least 6 h and from study medication for at least 12 h. Secondary outcomes were other lung function measurements, symptoms and rescue treatment use, the number of exacerbations, patient withdrawals, and disease-specific health status. We assessed adverse events, serum cortisol concentrations, skin bruising, and electrocardiograms. Analysis was as predefined in the study protocol.

Findings All active treatments improved lung function, symptoms, and health status and reduced use of rescue medication and frequency of exacerbations. Combination therapy improved pretreatment FEV_1 significantly more than did placebo (treatment difference 133 mL, 95% CI 105–161, p<0·0001), salmeterol (73 mL, 46–101, p<0·0001), or fluticasone alone (95 mL, 67–122, p<0·0001). Combination treatment produced a clinically significant improvement in health status and the greatest reduction in daily symptoms. All treatments were well tolerated with no difference in the frequency of adverse events, bruising, or clinically significant falls in serum cortisol concentration.

Interpretation Because inhaled long-acting β_2 agonists and corticosteroid combination treatment produces better control of symptoms and lung function, with no greater risk of side-effects than that with use of either component alone, this combination treatment should be considered for patients with COPD.

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See Commentary page 444

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity worldwide. It is characterised by chronic progressive symptoms, airflow obstruction,[1,2] and impaired health status,[3] which is worse in those who have frequent, acute episodes of symptom exacerbation.[4] The aim of treatment is to prevent and control symptoms and exacerbations while improving lung function and health status.[5,6] Any new treatment approach should be judged against these endpoints.

Inhaled long-acting β_2 agonists improve airflow obstruction, control of symptoms, and health status in patients with COPD over 3–4 months[7–14] and have several potentially beneficial non-bronchodilatory effects.[15] The role of inhaled corticosteroids in COPD management is less certain.[16] These drugs do not change the rate of decline in lung function,[17–20] but can increase postbronchodilator forced expiratory volume in 1 s (FEV_1),[17,19] reduce the number of exacerbations,[17,18] and slow the rate of decline in health status.[17] Whether long-acting β_2 agonists and inhaled corticosteroids in combination will result in treatment effects that are better than those associated with either drug alone is not clear. Furthermore, we do not know whether improvements seen in the short term will be maintained during sustained treatment. To test our hypothesis, we did a randomised controlled trial over 1 year of combination treatment with salmeterol and fluticasone versus each of the components and placebo.

Methods

Patients

We recruited outpatients with COPD from 196 hospitals in 25 countries. All patients had a baseline FEV_1 before bronchodilation that was 25–70% of that predicted, an increase of less than 10% of predicted FEV_1 30 min after inhaling 400 µg salbutamol, and a prebronchodilator FEV_1/forced vital capacity (FVC) ratio of 70% or less.[21] Patients also had a history of at least 10 pack-years of smoking (ie, equivalent to 20 cigarettes smoked per day for 10 years), of chronic bronchitis, at least one episode of acute COPD symptom exacerbation per year in the previous 3 years, and at least one exacerbation in the year immediately before trial entry that required treatment with oral corticosteroids, antibiotics, or both.

We excluded patients who had respiratory disorders other than COPD, required regular oxygen treatment, or had received systemic corticosteroids, high doses of inhaled corticosteroids (>1000 µg daily beclometasone dipropionate, budesonide, or flunisolide or >500 µg daily fluticasone), or antibiotics in the 4 weeks before the 2 week run-in period before the trial began.

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	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
Withdrawal after randomisation	140 (39 %)	119 (32 %)	108 (29 %)*	89 (25 %)†‡
Age	63·4 (8.6)	63.2 (8.6)	63.5 (8.5)	62.7 (8.7)
Male	269 (75 %)	261 (70 %)	260 (70 %)	270 (75 %)
Current smoker	171 (47 %)	191 (51 %)	198 (53 %)	186 (52 %)
Pack-years smoked	43·4 (22·4)	43·7 (21·9)	41·5 (20·7)	42·0 (22·4)
Previous ICS use	188 (52 %)	183 (49 %)	202 (54 %)	178 (50 %)
Previous LABA use	136 (38 %)	156 (42 %)	148 (40 %)	151 (42 %)
Pretreatment FEV_1 (% predicted)	44·2 (13·7)	44·3 (13·8)	45·0 (13·6)	44·8 (14·7)
Reversibility (% predicted FEV_1)	4·0 (4·5)	3·7 (4·3)	3·7 (3·9)	4·0 (4·7)
Pretreatment FEV_1 (mL)	1266 (467)	1245 (452)	1260 (449)	1308 (532)
Postbronchodilator FEV_1 (mL)	1379 (476)	1346 (463)	1363 (460)	1419 (549)
Pretreatment FVC (mL)	2500 (800)	2386 (751)	2443 (781)	2537 (838)
PEF L/min	243 (89)	235 (90)	246 (90)	247 (93)
SGRQ score	47·1 (16·5)	48·7 (17·1)	49·8 (15·8)	47·1 (15·7)
Median use of relief medication per day (range)	2·7 (0–17)	2·9 (0–14)	2·8 (0–15)	2·7 (0–11)
Mean number awakenings per week	3·5 (5·3)	3·5 (6·1)	3·5 (4·9)	2·8 (4·9)

ICS=inhaled corticosteroids. LABA=longacting β2 agonist. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. PEF=peak expiratory flow. SGRQ=St George's Respiratory Questionnaire. Data are number (%) or mean (SD) unless otherwise indicated. *p=0·007 vs placebo. †p=0·0001 vs placebo. ‡p=0·033 vs salmeterol.

Table 1: **Patients' demographic data and baseline characteristics**

We obtained approval from local ethics committees at each participating site, and all patients provided written informed consent.

Study design

We used a randomised, double-blind, placebo-controlled, parallel-group design. Recruited patients participated in a 2-week run-in to the trial, a 52-week treatment period with clinic visits at weeks 0, 2, 4, 8, 16, 24, 32, 40, and 52, and a 2-week post-treatment follow-up.

We used a randomisation schedule generated by the patient allocation for clinical trials (PACT) program to assign patients to study treatment groups. Every participating centre was supplied with a list of patient numbers (assigned to patients at their first visit) and a list of treatment numbers. Patients who satisfied the eligibility criteria were assigned the next sequential treatment number from the list. Salmeterol and fluticasone combination (50/500 μg twice daily), salmeterol (50 μg twice daily), fluticasone (500 μg twice daily) and placebo were packaged in identical inhaler devices. Study drugs were labelled in a way to ensure that both the patient and the investigator were unaware of the allocated treatment .

During the 2-week run-in, patients stopped taking regular inhaled corticosteroids or long-acting β_2 agonists. Inhaled salbutamol was used as relief medication throughout the study, and regular treatment with anticholinergics, mucolytics, and theophylline was allowed. All non-COPD medications could be continued if the dose remained constant whenever possible, and if their use would not be expected to affect lung function. If patients had clinically stable symptoms after 2 weeks, they were randomised to receive one of the following treatments: 50 μg salmeterol and 500 μg fluticasone in combination; 50 μg salmeterol; 500 μg fluticasone; or placebo, all twice daily, for 52 weeks via a multidose dry-powder inhaler (Diskus or Accuhaler [GlaxoSmithKline, Greenford, UK]).

The primary efficacy measure was FEV_1 after patients had abstained from all bronchodilators for at least 6 h, and from study medication for at least 12 h. Lung-

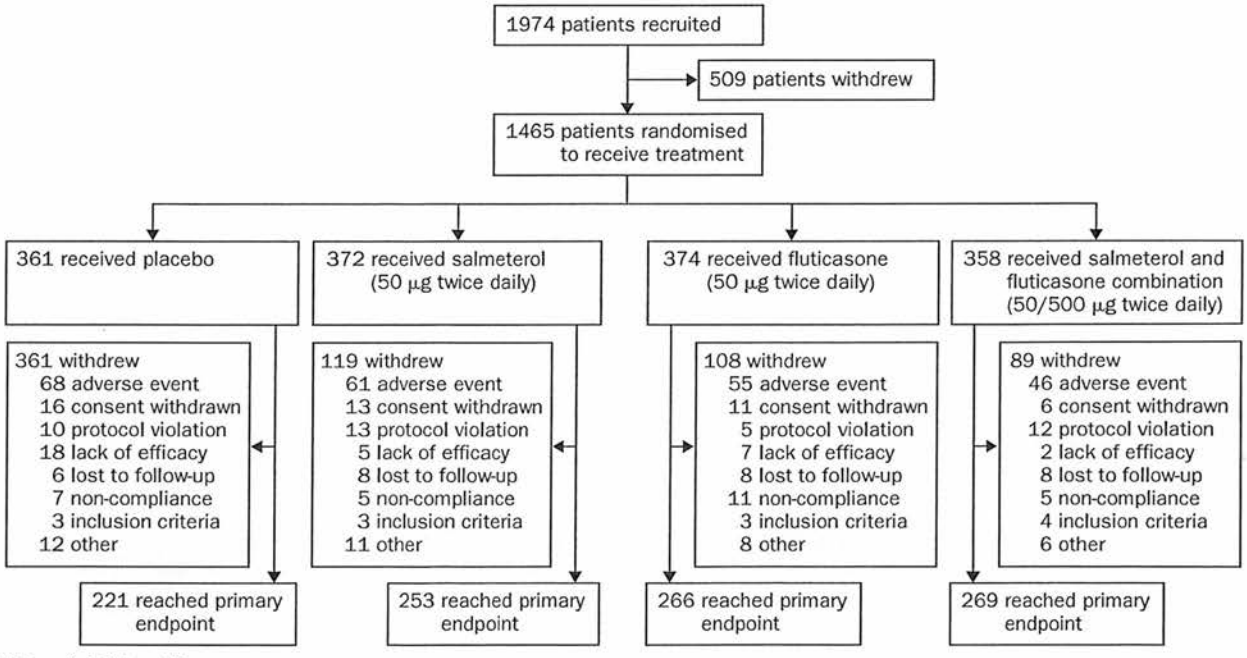

Figure 1: **Trial profile**

function tests were done in the clinic: pretreatment FVC, and postbronchodilator FEV_1 and FVC were measured at each visit. Postbronchodilator measurements were made 30 min after inhalation of 400 μg of salbutamol. All spirometry measurements were done at the same time of day for all patients, with the same spirometer. Every morning, patients used daily record cards to record the highest of three peak expiratory flow values measured with a mini-Wright peak flow meter (Clement Clarke International Harlow, UK) before medication.

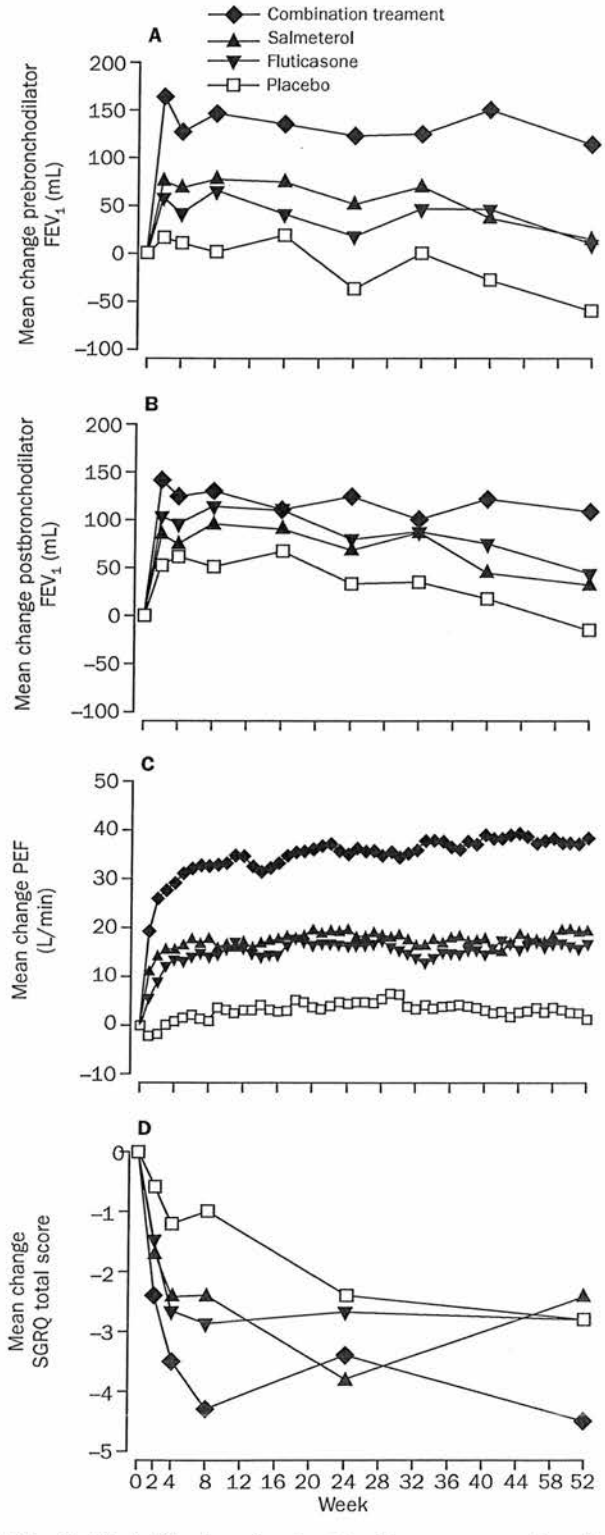

Figure 2: **Effect of treatment on lung function measurements and health status**

Raw mean changes from baseline are shown. A, prebronchodilator FEV_1. B, postbronchodilator FEV_1. C, daily peak expiratory flow. D, health status—the fall in St George's score represents an improvement in health status.

Every morning, patients recorded the number of times they used relief medication, their symptom scores, and the number of night-time awakenings for the previous 24 h. Symptoms were scored as: breathlessness, 0 (none) to 4 (breathless at rest); cough, 0 (none) to 3 (severe); sputum production, 0 (none) to 3 (severe); sputum colour, 0 (no sputum produced) to 4 (dark yellow or green).

The occurrence of acute exacerbations of COPD symptoms was investigated at every clinic visit. Exacerbations were defined a priori as a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both. Episodes that required corticosteroid treatment or hospital admission were noted separately. Health status was assessed with the St George's Respiratory Questionnaire at weeks 0, 2, 4, 8, 24, and 52. In the 22 non-English speaking countries we used a validated translation of this questionnaire.

Adverse event information was obtained at every clinic visit by recording spontaneously reported complaints from patients and asking general questions about medical troubles and concomitant medication. Morning (0800–1000 h) cortisol concentrations in serum were measured after fasting at weeks 0, 24, and 52. At every visit we noted the number of bruises on the volar side of the forearms that had a diameter greater than 5 cm. All patients had 12-lead electrocardiography at weeks 0, 24, and 52, and investigators categorised the results as normal, abnormal but not clinically significant, or abnormal and clinically significant.

Statistical analysis

We estimated that a sample size of 300 patients per treatment group would be needed to obtain data for 250 patients so as to detect a 0·10 L difference in FEV_1 at the 5% significance level with 90% power, assuming an SD of 0·35 L for FEV_1. We analysed pretreatment FEV_1 using repeated measures analysis.[22] Time was included as a categorical parameter and an unstructured variance-covariance matrix was fitted with SAS proc mixed software version 6.12. We also used these methods to analyse other lung function variables and questionnaire scores. We analysed log-transformed serum cortisol concentrations, morning peak expiratory flow, and mean symptom score during weeks 1–52 using analysis of covariance. The number of exacerbations was analysed by a maximum likelihood Poisson regression, with the amount of time a patient had had treatment as an offset variable. Covariates used for analyses, where applicable, were age, sex, country, baseline value (such as FEV, and FVC at randomisation), and smoking status. Interactions of treatment with all covariates were tested for pretreatment FEV_1, exacerbations, and health status questionnaire scores. For use of rescue medication, the median data for weeks 1–52 were analysed using the van Elteren extension to the Wilcoxon rank sum test,[23] stratified by smoking status, and the confidence limits calculated with the Hodges-Lehman method.[24] The number of withdrawals was analysed with the Cochran-Mantel-Haenszel test, stratified by smoking status, and time to withdrawal was analysed with Cox's proportional hazards model.

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
Pretreatment FEV_1 (mL)				
Adjusted mean	1264 (11)	1323 (11)*	1302 (11)†	1396 (11)
Treatment difference‡	133	73	95	
(95% CI)	(105–161)	(46–101)	(67–122)	
p‡	<0·0001	<0·0001	<0·0001	
Postbronchodilator FEV_1 (mL)				
Adjusted mean	1408 (11)	1436 (11)	1454 (11)§	1484 (11)
Treatment difference‡	76	48	31	
(95% CI)	(47–106)	(19–77)	(2–60)	
p‡	<0·0001	0·0014	0·039	
Pretreatment FVC (mL)				
Adjusted mean	2439 (19)	2525 (19)¶	2500 (18)‖	2594 (19)
Treatment difference‡	155	68	94	
(95% CI)	(106–204)	(20–117)	(46–142)	
p‡	<0·0001	0·006	<0·0001	
PEF (L/min)				
Adjusted mean	242 (2·1)	257 (2·0)*	255 (2·0)*	274 (2·1)
Treatment difference‡	32	17	18	
(95% CI)	(26–37)	(11–22)	(13–24)	
p‡	<0·0001	<0·0001	<0·0001	

Data are mean (SE). *p<0·0001 *vs* placebo; †p=0·0063 *vs* placebo; ‡*vs* combination treatment §p=0·002 *vs* placebo; ¶ p=0·0004 *vs* placebo; ‖ p=0·013 *vs* placebo.

Table 2: **Effect of 52 weeks' treatment on lung function**

Role of the funding source

The study sponsor, GlaxoSmithKline, was involved together with the principal investigators in the study design; the collection and analysis of data, which was made freely available to all the principal investigators; and the decision to submit the paper for publication.

Results

We recruited 1974 patients from 196 centres in 25 countries, of whom 1465 received treatment (figure 1). Demographic data, baseline characteristics, and compliance did not differ between groups, but the withdrawal rate did. Significantly fewer patients withdrew from the combination and fluticasone groups than from placebo and salmeterol groups (table 1). The main reason for differences in withdrawal was presence of adverse events. Patients in the combination group had a slightly higher mean prebronchodilator and postbronchodilator FEV_1 and fewer mean awakenings per week than did those in other groups. These minor imbalances in baseline data were accounted for in the statistical analyses since both baseline FEV_1 and mean night awakenings per week were used as covariates in analyses where appropriate.

The three active treatments increased pretreatment FEV_1 significantly compared with placebo (salmeterol/fluticasone p<0·0001; salmeterol p<0·0001; fluticasone p=0·0063; figure 2). This improvement was evident by week 2 and was sustained throughout treatment. The rise in FEV_1 associated with combination therapy was significantly greater than with either of its components separately (table 2, figure 2). By week 52, pretreatment FEV_1 in the combination group had increased by 10% compared with 2% in both the salmeterol and fluticasone groups, and had fallen by 3% in the placebo group. We noted the same trend for the other lung-function variables (figure 2). The treatment-by-smoking-status interaction for prebronchodilator FEV_1 was not significant (p=0·134), indicating that the difference between the treatment groups was unaffected by whether the participant continued to smoke, or not. Furthermore, the effects of treatment were not biased by unbalanced changes in smoking status between the treatment groups. During the 12-month study period, a total of 103 patients (6–7% in each treatment group) changed their smoking habit, with most of these giving up smoking.

Compared with placebo, all active treatments significantly reduced the number of exacerbations per patient per year and the number of exacerbations that needed treatment with oral corticosteroids (table 3). The rate of exacerbations fell by 25% in the combination group (p<0·0001) and by 20% (p=0·0027) and 19% (p=0·0033) in the salmeterol and fluticasone groups, respectively, compared with placebo. The treatment effect was more pronounced in patients with severe disease (ie, a baseline FEV_1 <50% of predicted), who showed a 30% reduction with the

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
Total exacerbation rate				
Mean rate per patient per year (SD)	1·30	1·04*	1·05*	0·97
Treatment ratio† (95% CI)	0·746	0·930	0·925	
	(0·643–0·865)	(0·801–1·080)	(0·797–1·073)	
p†	<0·0001	0·345	0·304	
Rate of exacerbations requiring oral corticosteroids				
Mean rate/patient/year	0·76	0·54‡	0·50§	0·46
Treatment ratio†	0·607	0·853	0·925	
	(0·500–0·736)	(0·699–1·039)	(0·755–1·133)	
p†	<0·0001	0·115	0·453	

*p=0·003 *vs* placebo. †*vs* combination treatment. ‡p=0·0003 *vs* placebo. §p=0·0001 *vs* placebo.

Table 3: **Effect of 52 weeks' treatment on exacerbation rate**

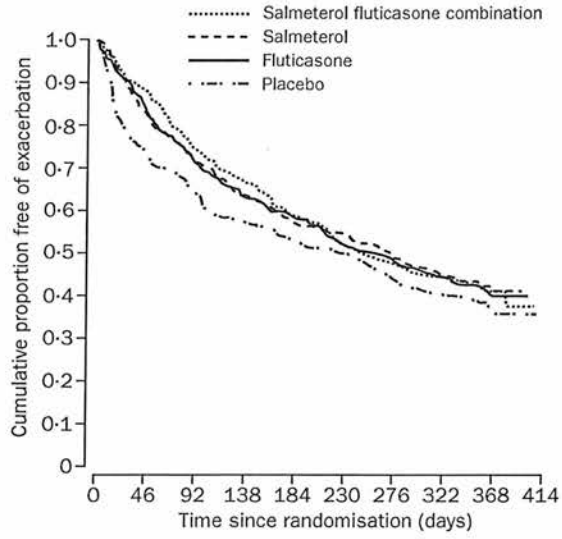

Figure 3: **Cumulative risk of acute exacerbations**

combination compared with placebo, as against a 10% reduction in patients who had a baseline FEV_1 that was greater than 50% of that predicted. Acute episodes of symptom exacerbation that required oral corticosteroids were reduced by 39% in the combination group (p<0·0001), 29% in the salmeterol group (p=0·0003), and 34% in the fluticasone group (p=0·0001), compared with placebo. There were no significant differences between active treatments with respect to their effect on the rate of episodes of symptom exacerbation (table 3), time to first exacerbation, or number of hospital admissions. Figure 3 shows the cumulative risk of acute exacerbations.

Combination treatment significantly reduced breathlessness and the use of relief medication compared with placebo, salmeterol, and fluticasone (table 4). Median number of days without relief medication was for placebo 0% (range 0–100%), salmeterol 3% (0–100%), fluticasone 2% (0–100%), and combination 14% (0–100%) (p<0·0001 *vs* placebo, p=0·004 *vs* salmeterol, p=0·0003 *vs* fluticasone). The number of night-time awakenings fell significantly in the combination group, compared with placebo and salmeterol, but not with fluticasone (table 4). Cough only improved significantly in the combination group (table 4).

Only the combination group showed a clinically significant improvement in health status questionnaire score by week 52. The raw mean changes in health status total score were −4·3 (SD 10·8) by week 8 and −4·5 (12·9) at week 52 (figure 2). The change in SGRQ score in the combination group over 52 weeks at the end of the study was significantly greater than that in both the placebo and fluticasone groups (table 4).

All treatments were well tolerated, and there were no differences between groups in the number of patients reporting an adverse event during treatment (78–81% across all groups), apart from an increased frequency of oropharyngeal candidosis (placebo 2%, salmeterol 2%, fluticasone 7%, combination 8%). Table 5 shows adverse events that were judged to be treatment-related. Most patients (≥96%) had serum cortisol values that were within the reference range, or that did not change significantly from baseline after 24 or 52 weeks of treatment. 13 (4%) and 11 (4%) patients in the placebo and salmeterol/fluticasone groups, respectively, had a change from within to below the reference range, compared with 17 (5%) and 19 (6%) in the salmeterol and fluticasone groups, respectively. None of these changes was clinically important. After 52 weeks' treatment, mean serum cortisol concentrations rose by 4% in placebo and 6% in the salmeterol group, whereas they fell by 1% with fluticasone and by 3% with the combination treatments. The differences between fluticasone and placebo were significant at weeks 24 (p=0·035) and 52 (p=0·007), and between combination and placebo at week 24 (p=0·020). None of the changes were associated with any clinical effects or signs of hypoadrenalism.

We noted skin bruises in a maximum of 22 (6%) of patients in the placebo group, 20 (6%) in salmeterol, 26 (7%) in fluticasone, and 29 (8%) in the combination group at any visit. We did not detect any changes on echocardiograms that could be attributed to treatment.

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
SGRQ total score				
Adjusted mean	46·3 (0·5)	45·2 (0·4)	45·5 (0·4)	44·1 (0·5)
Treatment difference* (95% CI)	−2·2 (−3·3 to −1·0)	−1·1 (−2·2 to 0·1)	−1·4 (−2·5 to −0·2)	
p*	0·0003	0·071	0·021	
Symptom scores				
Cough	1·44 (0·03)	1·36 (0·03)	1·38 (0·03)	1·35 (0·03)
p*	0·018	0·639	0·340	
Breathlessness	1·66 (0·03)	1·59 (0·03)	1·58 (0·03)	1·47 (0·03)
p*	0·0001	0·006	0·010	
Sputum production	1·34 (0·03)	1·30 (0·03)	1·33 (0·03)	1·29 (0·03)
p*	0·196	0·687	0·339	
Sputum colour	1·36 (0·03)	1·35 (0·03)	1·37 (0·03)	1·32 (0·03)
p*	0·373	0·494	0·250	
Median (range) use of relief medications (per day)	2 (0–32)	2 (0–14)†	2 (0–11)‡	1 (0–10)
p*	<0·0001	0·0001	0·0003	
Mean number awakenings per week	3·01 (0·21)	2·94 (0·21)	2·45 (0·21)§	2·31 (0·21)
p*	0·006	0·011	0·591	

SGRQ=St George's Respiratory Questionnaire. Data are mean (SE), unless otherwise indicated. A negative value represents an improvement in health status.
*vs combination; †p=0·028 *vs* placebo; ‡p=0·010 *vs* placebo; §p=0·024 *vs* placebo.

Table 4: **Effect of 52 weeks' treatment on health status and symptoms**

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
Any treatment-related event	49 (14%)	46 (12%)	70 (19%)	58 (16%)
Oropharyngeal candidosis	5 (1%)	5 (1%)	23 (6%)	22 (6%)
Candidosis in unspecified site	0	2 (<1%)	8 (2%)	1 (<1%)
Oral inflammation or nausea and vomiting	8 (2%)	3 (<1%)	3 (<1%)	4 (1%)
COPD exacerbation	19 (5%)	8 (2%)	10 (3%)	9 (3%)
Cough, breathing disorder, or lower respiratory infection	6 (2%)	7 (2%)	6 (2%)	3 (<1%)
Throat infection or hoarseness	8 (2%)	8 (2%)	16 (4%)	15 (4%)
Headaches, tremor, or vertigo	4 (1%)	10 (3%)	2 (<1%)	4 (1%)

Table 5: **Treatment-related adverse events**

Discussion

Ideally, any new treatment for COPD should improve one or more of the endpoints outlined in the GOLD (Global Initiative for Chronic Obstructive Lung Disease) management protocol[25]—symptoms, health status, and frequency of exacerbation. These effects should be sustained and better than those of existing treatments. Many treatment trials in COPD have only lasted 3–6 months,[18,26] or if longer, they have compared only one active treatment with placebo. Our trial has compared commonly prescribed agents from different therapeutic classes for a sufficient time to see changes in a range of clinically relevant outcomes. Our results confirm that active treatment is better than placebo. A combination of different types of treatment produces benefits across a range of endpoints that translate into a clinically noticeable benefit for patients, as indicated by the health status data.

Consistent changes were seen in the pretreatment FEV_1, suggesting a drug effect before the first dose taken in the day. Both salmeterol and fluticasone produced small but significant improvements in FEV_1 in keeping with previous findings,[7,17,18] but combination treatment was significantly more efficacious than either placebo or the individual components. Postbronchodilator FEV_1 improved after fluticasone, as also noted by investigators in the ISOLDE study.[17] Patients in the combination group had the lowest bronchodilator responsiveness (ie, the change between pretreatment and post-treatment FEV_1), suggesting that part of the pretreatment effect in patients in the combination group was caused by the bronchodilatory effects of salmeterol taken 12 h previously. However, despite this effect, patients in the combination group had a significantly higher postbronchodilator FEV_1 than with either agent alone. Data for FVC showed much the same trend as that seen for FEV_1, but are more relevant to improved exercise performance in COPD. Finally, the multiple daily readings of peak expiratory flow showed a sustained improvement throughout the year, which was significantly greater in the combination group, and evident within 1 week of randomisation. These early changes in lung function could provide a useful guide to subsequent patient benefit, but this indicator has not yet been formally tested.

Improved lung function was associated with reductions in the number and type of symptoms recorded in the daily diary cards. Although scores for cough and sputum did not change greatly, breathlessness was reduced by both salmeterol and fluticasone but significantly more so with combination treatment. Much the same pattern was seen with rescue treatment, and in the amount of sleep disruption. These data represent daily recordings for 1 year in every patient, and confirm the sustained nature of the clinical benefits. Health status measurement provides an integrated assessment of the effect of COPD on patients' health, and has been widely validated.[27,28] A 4-unit reduction in total St George's respiratory questionnaire score is associated with both subjective and objective improvement, such as the ability to walk further and less perceived breathlessness before and after exercise.[12,29,30] This improvement was achieved by patients in the combination treatment group after 12 months, but not by those who received single-drug treatment or placebo. The speed of change in health status was less striking than with lung-function tests but was still evident by 8 weeks, in keeping with other data about long-acting β2 agonists.[9] The lower than expected frequency of acute episodes of symptom exacerbation in patients who received placebo might explain some of the health status improvement.

All active treatments were associated with a lower rate of exacerbations than was placebo. Despite differences in definition, we noted a self-reported exacerbation rate that was similar to that in other trials—ie, 1·3 per year with placebo.[4,17] Combined treatment reduced the total exacerbation rate by 25% and exacerbations that required oral corticosteroids by 39%, which were all significant changes compared with placebo. Although these reductions were not statistically significant when compared with monotherapy, there was a trend in favour of the combination group which became more pronounced with increasing COPD severity. Despite our selection criteria, we saw substantially fewer exacerbations than expected (46% of patients did not have such an incident), which significantly reduced the power of the study to show a difference. The low rate of acute episodes might be attributable to regression to the mean in exacerbation number or an effect of improved care associated with clinical trials, but suggests that a study of longer duration and with a larger number of participants would be needed to show a difference. All active therapies were well tolerated, and there was no evidence of important cardiac side-effects with salmeterol, or any unanticipated problems with fluticasone. There were minor changes in cortisol secretion with fluticasone monotherapy and with combination treatment, which did not differ from those previously reported.[17,18]

The reasons why combination treatment proved to be most effective remain speculative. Results from research in asthma suggest that long-acting β_2 adrenoceptor agonists can enhance the anti-inflammatory effect of corticosteroids.[31] Although the absolute changes in lung function induced by combination treatment in our study were modest, they did happen rapidly, and were noticeable after 2 weeks. Such improvements could be sufficient to allow improvement in exercise tolerance and reduce the perceived severity of an exacerbation, and hence the number of episodes reported. Both factors are important determinants of health status.[17,32] The additional effect of an inhaled corticosteroid on

postbronchodilator FEV_1 has been noted before.[17] β receptor numbers can be upregulated with corticosteroids, and the combination is more effective in reducing induced interleukin 8 release from airway smooth muscle.[33] Whether this mechanism is important in COPD remains to be established

Contributors

P Calverley, R Pauwels, J Vestbo, A Gulsvik, P Jones, and N Pride, designed the study, reviewed the analysed data, and wrote the manuscript. C Madden designed the study, interpreted results, and helped to write the manuscript. J A Anderson analysed data, interpreted results, and helped to write the manuscript.

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Conflict of interest

P Calverley, R Pauwels, J Vestbo, A Gulsvik, P Jones, and N Pride have been consultants for, and received research grants from, GlaxoSmithKline. J Vestbo is married to an employee of GlaxoSmithKline. J Anderson and C Madden are employees of GlaxoSmithKline and hold shares in the company.

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Uses of error

The right word

G Burnham

Error is a grim idea, with connotations of bias, misjudgment, and increasingly, of liability. Yet the inadvertent and the fortuitous have given medicine a number of its great successes. Many of the errors noted in this *Lancet* series have centred on lessons practitioners have learnt from clinical misjudgments. Fewer have come from public health or population-based endeavours. As with clinical medicine, these chance occurrences are both prevalent and underacknowledged.

When ivermectin was first being tested for effectiveness in onchocerciasis we set out to measure its adverse reactions when given as mass treatment. The three-year study was conducted in an endemic area of Malawi using a double blind, placebo-controlled design. For these multi-site trials, the World Health Organization had set explicit criteria for exclusion of subjects from the study. Because of the potential for ivermectin to cross the blood-brain barrier in mice, it was thought that persons with a history of epileptic fits should not receive treatment. This was an important consideration for us since epilepsy was quite common in this part of Malawi, and our hospital ran a heavily patronised outreach service for its treatment.

Instructions for potential ivermectin recipients were translated into the vernacular, back translated, and then pilot tested in a nearby non-study site for comprehension. Changes were made as necessary to instructions. The importance of epilepsy as a reason for not participating was specifically noted in the verbal instructions to potential participants.

After the first round of treatment it became evident that almost no one had been excluded from treatment because of a history of epilepsy. Pursuing this it was discovered that the specific word used for epilepsy was not recognised in the study villages even though the language was the same as in the pilot area where the instructions had been pre-tested. In a hurried follow-up we identified some 80 persons with epilepsy who had been unintentionally treated with ivermectin. Further investigations in this cohort with a history of epilepsy revealed that no fits had followed treatment. The cohort was then followed through the two subsequent annual treatment rounds during which there was no association between receiving treatment and having fits. On the basis of these Malawi findings, a history of epilepsy was dropped as a reason for excluding treatment in the subsequent ivermectin mass-treatment programmes for onchocerciasis. The outcome from this error of words has been that tens of thousands of epileptics living in 37 countries where onchocerciasis is endemic have been treated regularly as a prevention against this physically disabling and potentially blinding disease. This is another reminder that a study may yield important findings aside from the answering of the original research questions.

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Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease

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Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. P.M. Calverley, W. Boonsawat, Z. Cseke, N. Zhong, S. Peterson, H. Olsson. ©ERS Journals Ltd 2003.

ABSTRACT: Lung function in chronic obstructive pulmonary disease (COPD) can be improved acutely by oral corticosteroids and bronchodilators. Whether clinical improvement can be maintained by subsequent inhaled therapy is unknown.

COPD patients (n=1,022, mean prebronchodilator forced expiratory volume in one second (FEV1) 36% predicted) initially received formoterol (9 μg *b.i.d.*) and oral prednisolone (30 mg *o.d.*) for 2 weeks. After this time, patients were randomised to *b.i.d.* inhaled budesonide/formoterol 320/9 μg, budesonide 400 μg, formoterol 9 μg or placebo for 12 months.

Postmedication FEV1 improved by 0.21 L and health-related quality of life using the St George's Respiratory Questionnaire (SGRQ) by 4.5 units after run-in. Fewer patients receiving budesonide/formoterol withdrew from the study than those receiving budesonide, formoterol or placebo. Budesonide/formoterol patients had a prolonged time to first exacerbation (254 *versus* 96 days) and maintained higher FEV1 (99% *versus* 87% of baseline), both primary variables *versus* placebo. They had fewer exacerbations (1.38 *versus* 1.80 exacerbations per patient per year), had higher prebronchodilator peak expiratory flow, and showed clinically relevant improvements in SGRQ *versus* placebo (-7.5 units). Budesonide/formoterol was more effective than either monocomponent in both primary variables.

Budesonide/formoterol in a single inhaler (Symbicort®) maintains the benefit of treatment optimisation, stabilising lung function and delaying exacerbations more effectively than either component drug alone or placebo.

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Several randomised, controlled trials have shown that long-acting, inhaled β_2-agonists improve lung function in chronic obstructive pulmonary disease (COPD) irrespective of disease severity [1], and improve health-related quality of life (HRQL) [2, 3]. These improvements equal or exceed those seen with ipratropium [3] or theophylline [4]. Only two studies have followed the effects of treatment with long-acting, inhaled β_2-agonists over 1 yr [5, 6]. The results confirmed the effect on spirometry, but the change in HRQL was smaller than expected.

The role of inhaled corticosteroids (ICS) in COPD is more controversial. Corticosteroids do not appear to affect the rate of decline of forced expiratory volume in one second (FEV1) [7–10]. However, ICS increased postbronchodilator FEV1 in two studies [8, 9], and reduced the severity [11] and frequency of exacerbations when this end-point could be reliably assessed [9]. These observations have led to ICS being recommended for COPD patients with FEV1 <50% predicted who show a spirometric response [12]. In two 1-yr studies, the clinical effect of ICS on exacerbations requiring oral steroids was confirmed [5, 6]; the reduction in exacerbation frequency was less evident for patients taking ICS alone in the study by SZAFRANSKI *et al.* [5]. These results may suggest that sicker patients require more than just ICS in their treatment for COPD.

For editorial comments see page 874.

Combining a long-acting β_2-agonist and an ICS as maintenance therapy has been very successful in managing bronchial asthma [13, 14], but less is known about this treatment strategy in COPD. Lung function (prebronchodilator FEV1) is improved when these drugs are combined, compared with monotherapy [15], and recent studies have found that combining therapies is also associated with fewer exacerbations and improved HRQL, compared with placebo treatment [5, 6].

Patients with more severe COPD (Global Initiative for Obstructive Lung Disease (GOLD) stages III and IV) frequently experience exacerbations, which impact on their HRQL [16]. Prolonging the time to exacerbation may delay the deterioration of the disease and help maintain health status, an important aim in the treatment of COPD. Moreover, it can be difficult to separate the improvement in health status that occurs at the start of a clinical trial, due to closer medical attention, from the effects of treatment itself, and this caveat can reduce the power of the study to assess the true therapeutic effect on this outcome. To address this difficulty, a clinical trial was conducted in which inhaled formoterol and oral corticosteroids were administered during a short run-in period, to ensure that patients' treatment was optimised before entry into the trial. During the 12-month, randomised treatment period in patients with COPD, an ICS (budesonide) and a long-acting β_2-agonist (formoterol) given in the same inhaler were compared with the component drugs given

separately and with placebo. The primary outcomes were time to first exacerbation and change in FEV1. Data were also recorded on HRQL, peak expiratory flow (PEF), symptoms, use of reliever medication and adverse events (AEs). This protocol allowed the authors to test a clinically relevant situation, namely whether the short-term improvement that follows a period of treatment optimisation can be maintained over a longer time by inhaled therapy, and to investigate which drugs change what aspect of patient well-being.

Methods

Patients

Outpatients with COPD (GOLD stages III and IV) [12] were recruited based on the following criteria: aged ⩾40 yrs, COPD symptoms for >2 yrs, smoking history of ⩾10 pack-yrs, FEV1/vital capacity (VC) ⩽70% prebronchodilator, FEV1 ⩽50% of predicted normal value prebronchodilator, using inhaled bronchodilators as reliever medication, ⩾1 COPD exacerbation requiring a course of oral corticosteroids and/or antibiotics 2–12 months before the first clinic visit.

Principal exclusion criteria were: a history of asthma/seasonal allergic rhinitis before the age of 40 yrs, any relevant cardiovascular disorders or significant disease/disorder, which may have put patients at risk or influenced the results of the study, an exacerbation of COPD requiring medical intervention within 4 weeks prior to enrolment and/or during run-in, use of oxygen therapy, β-blocking agents or nonallowed medications. All patients gave written, informed consent and the study was approved by an Ethics Committee for each centre.

Study design

This was a randomised, double-blind, placebo-controlled, parallel-group study involving 109 centres in 15 countries or regions. All medication was from AstraZeneca, Lund, Sweden, and delivered *via* a dry powder inhaler (Turbuhaler®; AstraZeneca). During the 2-week run-in, patients received oral prednisolone (30 mg) *o.d.* and inhaled formoterol (Oxis®) 2×4.5 μg *b.i.d.*, and terbutaline (Bricanyl®) 0.5 mg as needed. Patients were then randomised to 12 months of treatment with either budesonide (Pulmicort®) 2×200 μg *b.i.d.*, formoterol 2×4.5 μg *b.i.d.*, budesonide/formoterol (Symbicort®; this Turbuhaler® delivers the same amount of budesonide and formoterol as the corresponding Turbuhaler® monoproducts) 2×160/4.5 μg *b.i.d.*, or placebo (lactose monohydrate) *b.i.d* with terbutaline 0.5 mg as needed.

Certain medications were allowed, with restrictions, after randomisation. Courses of oral corticosteroids (maximum 3 weeks per course) and antibiotics were allowed in the event of exacerbations. Parenteral steroids and/or nebulised treatment (single injections/inhalations) were allowed at emergency visits.

The following medications were disallowed from recruitment: inhaled steroids (except the study medication), disodium cromoglycate, leukotriene antagonists or 5-lipoxygenase (5-LO) inhibitors, bronchodilators (other than study medication and terbutaline 0.5 mg (Bricanyl®) as needed), antihistamines, any medication containing ephedrine, and β-blockers, including eye-drops.

The following medications were withheld prior to recruitment: short-acting inhaled or oral β_2-agonists (6 h before), inhaled or oral long-acting β_2-agonists (48 h), inhaled short-acting anticholinergics (8 h), inhaled long-acting anticholinergics (7 days), xanthine-containing derivatives *o.d.* (48 h), xanthine-containing derivatives *b.i.d.* (24 h), leukotriene antagonists or 5-LO inhibitors (48 h).

Assessments

Patients attended the clinics at recruitment, randomisation and after 1, 2, 3, 6, 9 and 12 months of treatment. The primary variables were time to first exacerbation and change in post-medication FEV1. The secondary variables were number of exacerbations, time to and number of oral corticosteroid-treated episodes, morning and evening PEF, slow VC, HRQL, symptoms, use of reliever medication and AEs.

Exacerbations requiring medical intervention (oral antibiotics and/or corticosteroids or hospitalisation) were recorded at each visit after randomisation. The time to and number of exacerbations and oral corticosteroid-treated episodes were analysed.

Predicted FEV1 was calculated at recruitment using European Respiratory Society (ERS) equations [17]. FEV1 was measured before and 15 min after two inhalations of terbutaline 0.5 mg and the per cent increase from baseline in FEV1 was calculated. Spirometry (FEV1 and slow VC) measured after study medication and at least 6 h postreliever, at each clinic visit, met ERS standards [17]. Wherever possible, spirometry was performed at the same time of day, using the same spirometer (calibrated on each study day in accordance with the trademark specification), and supervised by the same well-trained study staff. Patients were instructed to rest for 15 min before measurement and spirometry was performed in a sitting position whilst wearing a noseclip. All spirometers met or exceeded the American Thoracic Society recommendations.

Prebronchodilator PEF, measured using a Mini-Wright® peak flow meter (Clement Clark, Harlow, UK), was recorded daily in a diary, in the morning and evening as the best of three attempts before inhalation of the study medication.

The St George's Respiratory Questionnaire (SGRQ) [18] was used to assess HRQL. Questionnaires were completed at recruitment, at randomisation, and at 6 and 12 months; a Total score was calculated. A lower score indicates better health, while a change of ⩾4 units indicates the minimal clinically important difference relevant to the patient [19]. Symptoms of shortness of breath, cough, chest tightness and night-time awakenings (on a 5-point scale from 0 (none, unaware of symptoms) to 4 (severe)), as well as use of reliever medication, were recorded daily in a patient diary. AEs were monitored at each postrandomisation visit by asking a standard question.

Analysis

With 150 patients per group, a difference in survival curves could be detected with 80% power if 66% exacerbated in the reference group and 50% in the comparative group. Adjusting for a 35% dropout rate implied ~230 patients per group.

An intention-to-treat analysis was used and all hypothesis testing was with two-sided alternative hypotheses; $p<0.05$ was considered statistically significant. Time to first exacerbation was analysed using a log-rank test and described further by hazard rates from a Cox proportional hazards model, with treatment as factor and stratifying by country. The number of exacerbations was analysed using a Poisson regression model (expressed as mean rate *i.e.* mean number of exacerbations per patient per year). Treatment and country were used as factors, time in study as an offset variable, and confidence intervals were adjusted for overdispersion. Oral corticosteroid

courses were analysed similarly to exacerbations. The FEV1 and VC end-points were the mean of all available measurements during the treatment period, analysed in a multiplicative analysis of variance (with logarithm of values) with treatment and country as factors, and the randomisation value as a covariate. The mean ratios were presented as per cent increases. Both primary variables were required to give statistical significance at the 5% level in order to keep the overall significance level to 5% in the final conclusion [20]. Differences in subgroup response were addressed using standard "treatment by subgroup" interaction analyses. SGRQ was analysed in a similar manner to FEV1 but based on the last available measurement on treatment. Diary-card variables were also analysed in a similar manner to FEV1 but with an additive model.

Results

Patients

Of 1,141 patients enrolled into the study, 119 (10%) withdrew during run-in; 26% of these were due to COPD worsening and 24% due to AEs other than COPD worsening. Following run-in, 1,022 patients were randomised, of whom 629 (62%) completed the study (table 1). Mean demographic and baseline characteristics were similar across all treatment groups (table 2) and correspond in general to GOLD stages III and IV COPD [12]. After the initial period of treatment optimisation, the group mean FEV1 had increased by (mean±SD) 0.21±0.32 L and the SGRQ Total score decreased by 4.5±10.7 units.

Withdrawal from study

The budesonide/formoterol group had a lower risk of withdrawing from the study compared with the placebo, budesonide and formoterol groups (table 1). There was no significant difference in withdrawal rates *versus* placebo in either the budesonide group or the formoterol group.

After randomisation, 393 patients withdrew from the study; 193 of these were due to COPD worsening, 72 withdrew because of AEs other than COPD worsening, and 128 for other reasons (table 1). Significantly fewer withdrawals due to COPD worsening were reported in the budesonide/formoterol

Table 1.–Patient flow and withdrawals

	B/F	B	F	Placebo	Total
Patients enrolled					1141
Patients withdrawn during run-in					119
Patients randomised	254	257	255	256	1022
Patients withdrawn after randomisation[#]	74 (29)	102 (40)	111 (44)	106 (41)	393 (38)
Patients withdrawn due to COPD worsening[¶]	28 (11)	46 (18)	59 (23)	60 (23)	193 (19)
Patients withdrawn due to adverse event other than COPD worsening	20 (8)	21 (8)	20 (8)	11 (4)	72 (7)
Patients lost to follow-up	0 (0)	2 (0.8)	3 (1.2)	3 (1.2)	8 (0.8)
Eligibility criteria not fulfilled	4 (1.6)	4 (1.6)	4 (1.6)	6 (2.3)	18 (1.8)
Other reasons	22 (8.7)	29 (11.3)	25 (9.8)	26 (10.2)	102 (10.0)
Patients completing study	180 (71)	155 (60)	144 (56)	150 (59)	629 (62)

Data are presented as n (% of randomised patients per group) unless otherwise stated. B: budesonide; F: formoterol; COPD: chronic obstructive pulmonary disease. [#]: p=0.001 budesonide/formoterol *versus* placebo, p=0.037 budesonide/formoterol *versus* budesonide, p<0.001 budesonide/formoterol *versus* formoterol, p=0.223 budesonide *versus* placebo, p=0.950 formoterol *versus* placebo (Cox proportional hazards model); [¶]: p<0.001 budesonide/formoterol *versus* placebo and *versus* formoterol, p=0.038 budesonide/formoterol *versus* budesonide, p=0.031 budesonide *versus* placebo, p=0.616 formoterol *versus* placebo (Cox proportional hazards model).

Table 2.–Patient demographic and baseline characteristics (at enrolment, unless otherwise stated)

	B/F	B	F	Placebo
Patients randomised n	254	257	255	256
Male %	78	74	75	75
Age yrs	64 (42–86)	64 (41–85)	63 (41–84)	65 (43–85)
Current smokers %	33	39	36	30
Pack-yrs	39 (10–240)	39 (10–150)	38 (10–120)	39 (10–150)
Previous medication % of patients				
ICS	47	51	48	46
Inhaled SABAs	52	49	53	48
Anticholinergics	29	30	30	32
Inhaled LABAs	31	30	30	25
Xanthines	37	33	40	36
Inhaled combination of β_2-agonist and anticholinergic	16	18	18	22
FEV1 L	0.98±0.33	0.99±0.33	1.00±0.32	0.98±0.33
FEV1 % predicted	36±10	36±10	36±10	36±10
FEV1/VC %	42±12	44±12	44±12	44±11
Reversibility % predicted	6±7	6±7	6±6	6±6
Baseline SGRQ Total score at randomisation	48±19	49±18	47±19	48±18

Data are presented as mean (range) or mean±SD unless otherwise stated. B: budesonide; F: formoterol; ICS: inhaled corticosteroid; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; FEV1: forced expiratory volume in one second; VC: vital capacity; SGRQ: St George's Respiratory Questionnaire.

group compared with the placebo, budesonide and formoterol groups (table 1).

Exacerbations

Budesonide/formoterol prolonged time to first exacerbation compared with all other treatments (all $p<0.05$, log-rank test; fig. 1). Hazard rate analysis showed that the risk of having an exacerbation while being treated with budesonide/formoterol was reduced by 22.7%, 29.5% and 28.5% *versus* budesonide, formoterol and placebo, respectively. The exacerbation rate with budesonide/formoterol was reduced compared with placebo (23.6%) and formoterol (25.5%) but not with budesonide alone (13.6%) (table 3). Neither budesonide nor formoterol affected either measure of exacerbation compared with placebo.

When the analysis was restricted to oral corticosteroids given due to exacerbations, the lowest rates were found in the budesonide/formoterol and budesonide treatment groups (table 3). Budesonide/formoterol prolonged the time to first course of oral corticosteroids after randomisation; risk reductions were 32.7% and 33.8% *versus* budesonide and formoterol, respectively (both $p<0.01$), and 42.3% *versus* placebo ($p<0.001$). Budesonide/formoterol also reduced the rate of oral corticosteroid courses by 28.2%, 30.5% and 44.7% *versus* budesonide, formoterol and placebo, respectively; budesonide alone reduced the number of oral corticosteroid courses compared with placebo but formoterol did not (table 3).

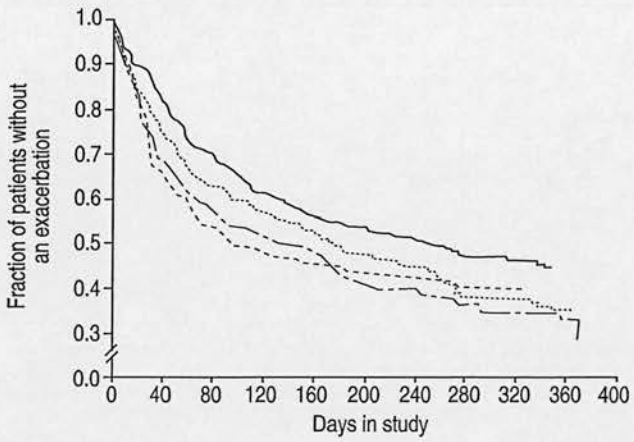

Fig. 1.–Kaplan-Meier plot of time to first exacerbation by treatment group. Log-rank tests of budesonide/formoterol (——) *versus* budesonide (·····), p=0.037; budesonide/formoterol *versus* formoterol (— -), p=0.002; budesonide *versus* placebo (- - -), p=0.796; formoterol *versus* placebo, p=0.490; and budesonide/formoterol *versus* placebo, $p<0.05$.

Lung function

After the optimisation period, the improvement in FEV1 seen during run-in was maintained with budesonide/formoterol treatment throughout the study. In contrast, FEV1 declined greatly and rapidly with all other treatments. This difference was significant with budesonide/formoterol compared with placebo (14%), budesonide (11%) and formoterol (5%), and with formoterol *versus* placebo (8%), but not with budesonide *versus* placebo (2%) (fig. 2).

Changes in VC closely followed those of FEV1. Budesonide/formoterol and formoterol improved VC *versus* placebo (both $p<0.001$), while budesonide/formoterol also improved VC *versus* budesonide ($p<0.001$). Budesonide/formoterol therapy was also associated with higher morning PEF compared with all other treatments, and higher evening PEF compared with placebo and budesonide (fig. 3).

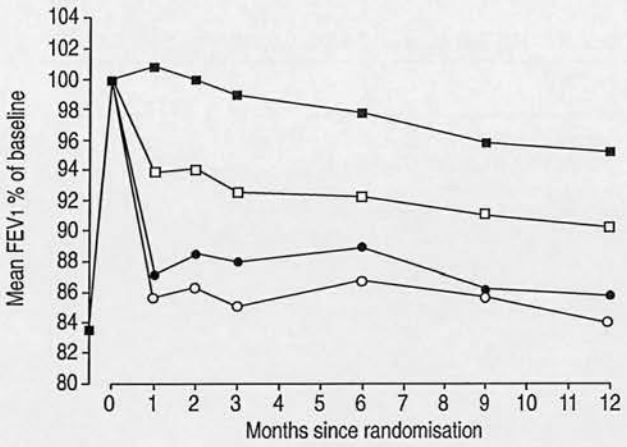

Fig. 2.–Changes in mean forced expiratory volume in one second (FEV1) in the four treatment groups from randomisation to the average of all available measurements during the 12-month treatment period. Budesonide/formoterol (■) *versus* budesonide (●), $p<0.001$; budesonide/formoterol *versus* formoterol (□), p=0.002; budesonide *versus* placebo (○), p=0.145; formoterol *versus* placebo, $p<0.001$; budesonide/formoterol *versus* placebo, $p<0.001$.

Table 3.–Analysis of exacerbations and oral corticosteroid courses due to exacerbations

	B/F	B	F	Placebo
Time to first exacerbation				
Median number of days	254	178	154	96
#RR (95% CI) B/F *versus* other groups+		0.773 (0.611–0.980)*	0.705 (0.558–0.891)**	0.715 (0.562–0.910)
p-value¶	0.006	0.512	0.901	
Total number of exacerbations				
Mean rate per patient per year	1.38	1.60	1.85	1.80
RR (95% CI) B/F *versus* other groups+		0.864 (0.679–1.100)	0.745 (0.587–0.945)*	0.764 (0.600–0.973)
p-value¶	0.029	0.308	0.828	
Exacerbations requiring oral corticosteroids				
Mean rate per patient per year	0.63	0.87	0.91	1.14
RR (95% CI) B/F *versus* other groups+		0.718 (0.543–0.949)*	0.695 (0.523–0.923)*	0.553 (0.420–0.728)
p-value¶	<0.001	0.044	0.085	

B: budesonide; F: formoterol; RR: rate ratio; CI: confidence interval. #: a RR of 0.715 represents a reduction in rate of 28.5%; ¶: *versus* placebo; +: rates from Poisson regression model, RR is hazard ratio from Cox proportional hazards model. *: $p<0.05$ in favour of budesonide/formoterol; **: $p<0.01$ in favour of budesonide/formoterol.

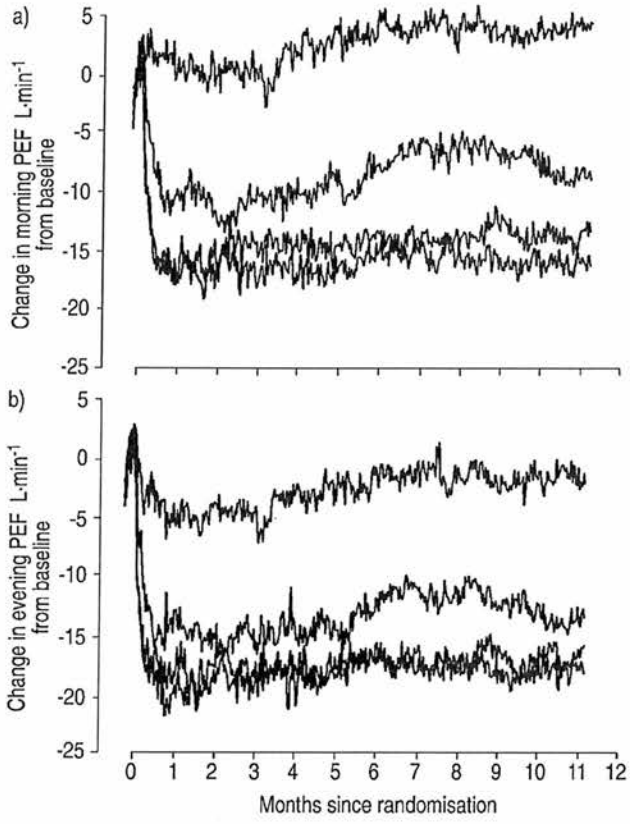

Fig. 3.–Change in peak expiratory flow (PEF) from randomisation to the average of all available measurements during the 12-month treatment period (from daily diary-card data). Budesonide/formoterol (top line) therapy was associated with a) higher morning PEF *versus* placebo (bottom line; 18 L·min^{-1} difference, p<0.001), budesonide (line third from top; 15 L·min^{-1}, p<0.001) and formoterol (line second from top; 7 L·min^{-1}, p=0.007). Formoterol *versus* placebo p<0.001. b) Budesonide/formoterol therapy was associated with higher evening PEF *versus* placebo (14 L·min^{-1}, p<0.001) and budesonide (12 L·min^{-1}, p<0.001), but not *versus* formoterol (5 L·min^{-1}) and this improvement was sustained throughout the treatment phase. Formoterol was also associated with placebo (p<0.001).

For both exacerbations and FEV1, interaction analyses between treatment and sex, smoking status/history, reversibility or use of ICS at entry, were performed in order to investigate differences in treatment response. There was no evidence of heterogeneity in the treatment differences with respect to the primary variables in any of these categories, *i.e.* the results in these groups were consistent with the main analysis.

Health-related quality of life

Baseline values for the SGRQ Total score were similar in each group and high, indicating poor HRQL (table 2). At the end of the run-in period, Total scores had improved by a mean of 4.5 units (range 3.6–4.8; fig. 4). During the treatment period, the Total scores fell further in the budesonide/formoterol group, representing an additional improvement beyond that achieved during run-in. Treatment with budesonide or formoterol allowed the initial improvement in HRQL to be maintained, while HRQL in the placebo group deteriorated to the original (prerun-in) values (fig. 4). Thus,

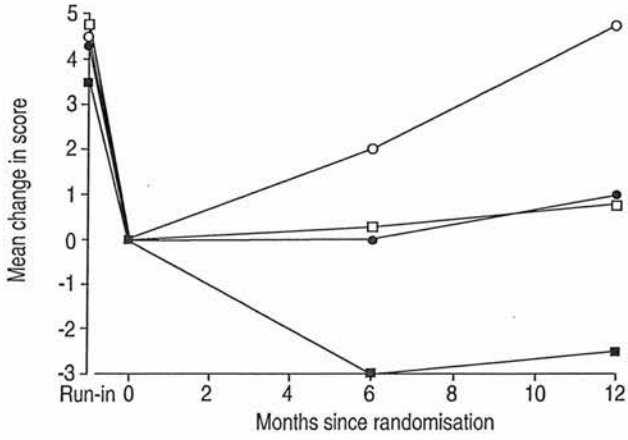

Fig. 4.–Time course of the change in St George's Respiratory Questionnaire Total scores relative to first attendance measured at clinic visits. At 12 months, budesonide/formoterol (■) *versus* budesonide (●), p=0.001; budesonide/formoterol *versus* formoterol (□), p=0.014; budesonide *versus* placebo (○), p<0.05; formoterol *versus* placebo, p<0.01; and budesonide/formoterol *versus* placebo, p<0.001.

all active treatments improved the Total score *versus* placebo, with the greatest improvement occurring with budesonide/formoterol (differences at 12 months of -7.5, -3.0 and -4.1 *versus* placebo for budesonide/formoterol, budesonide and formoterol, respectively). Similarly, Symptoms, Activity and Impacts domain scores were each improved by ⩾5.5 units in those patients receiving budesonide/formoterol compared with the placebo group (p<0.01). In addition, budesonide/formoterol showed improvements *versus* monocomponents in the Activity (changes of -3.6 *versus* budesonide and -3.5 *versus* formoterol, both p<0.05) and Impacts (changes of -5.7 (p<0.001) *versus* budesonide, and -3.7 (p<0.05) *versus* formoterol) domains, but not in the Symptoms domain (-2.8 *versus* budesonide and -0.6 *versus* formoterol).

Symptoms

Budesonide/formoterol and formoterol improved the total symptom score and the individual symptom scores for shortness of breath, chest tightness and night-time awakenings compared with placebo. Budesonide also improved the night-time awakenings score compared with placebo. None of the treatments significantly improved the cough score. Mean data for changes from run-in to end of treatment in symptom scores and differences between groups are shown in table 4.

Use of reliever medication

Budesonide/formoterol significantly reduced the use of reliever medication by 0.8 inhalations per day *versus* both budesonide and placebo (both p<0.001), and by 0.3 inhalations per day *versus* formoterol (p<0.05), and formoterol reduced reliever medication intake by 0.4 inhalations per day *versus* placebo (p<0.01). Budesonide alone had no effect on this variable compared with placebo.

Safety

No further safety issues for budesonide/formoterol were identified in this study compared with what is previously

Table 4.–Mean changes from run-in to end of treatment in symptom scores

	Total symptom score (0–16)	Shortness of breath score (0–4)	Chest tightness score (0–4)	Cough score (0–4)	Night-time awakening score (0–4)
B/F *versus* placebo	-0.56 (-0.89–-0.24)	-0.21 (-0.32–-0.10)	-0.16 (-0.26–-0.05)	-0.07 (-0.17–0.03)	-0.16 (-0.27–-0.05)
p-value	<0.001	<0.001	0.004	0.180	0.004
B/F *versus* B	-0.26 (-0.58–-0.07)	-0.12 (-0.23–-0.01)	-0.09 (-0.20–0.01)	-0.02 (-0.12–0.08)	-0.05 (-0.16–0.06)
p-value	0.120	0.040	0.080	0.651	0.361
B/F *versus* F	-0.02 (-0.35–0.30)	0.00 (-0.11–0.11)	-0.01 (-0.12–0.09)	-0.02 (-0.12–0.08)	-0.04 (-0.15–0.07)
p-value	0.891	0.946	0.788	0.705	0.463
B *versus* placebo	-0.30 (-0.63–0.02)	-0.09 (-0.20–0.02)	-0.06 (-0.17–0.04)	-0.05 (-0.15–0.05)	-0.11 (-0.21–-0.00)
p-value	0.067	0.100	0.238	0.372	0.049
F *versus* placebo	-0.54 (-0.87–-0.21)	-0.21 (-0.32–-0.10)	-0.14 (-0.25–-0.04)	-0.05 (-0.15–0.05)	-0.12 (-0.22–-0.01)
p-value	0.001	<0.001	0.008	0.335	0.033

Data are presented as mean (95% confidence interval) unless otherwise stated. B: budesonide; F: formoterol.

known for budesonide/formoterol, budesonide and formoterol in COPD and asthma. The mean number of AEs experienced with budesonide/formoterol was no different from that with placebo (5, 5, 6 and 5 AEs per 1,000 treatment days for the budesonide/formoterol, budesonide, formoterol and placebo groups, respectively), and the most frequently reported AEs were similar across the treatment groups (table 5). The lowest number of withdrawals was in the budesonide/formoterol group (table 1) and the lowest number of serious AEs other than deaths were in the budesonide/formoterol and placebo groups (65, 88, 85 and 66 in the budesonide/formoterol, budesonide, formoterol and placebo groups, respectively). The number of serious AEs related to COPD was 40, 40, 55 and 38 in the budesonide/formoterol, budesonide, formoterol and placebo groups, respectively. The numbers of deaths were 5, 6, 13 and 5 in the budesonide/formoterol, budesonide, formoterol and placebo groups, respectively. Most of the deaths were events related to COPD and only a few were related to cardiovascular events.

Discussion

Many clinicians manage newly referred COPD patients by intensifying their treatment, often including a period of oral corticosteroid therapy with the hope of selecting individuals who are "corticosteroid responders". A substantial number of patients show spirometric improvements with either a β_2-agonist or oral corticosteroids, or both [21]. Unfortunately, neither the presence of a "positive" or "negative" oral corticosteroid response in patients with more severe COPD predicts future response to inhaled therapy [9]. Whether these improvements in lung function are accompanied by changes in symptomatic end-points like HRQL has not been studied, nor has the ability of inhaled drugs to maintain these effects been assessed, although results from observational studies suggest that at least ICS may be beneficial [22]. This study shows that significant short-term improvements in lung function (both FEV1 and PEF) and HRQL occur after optimised treatment with formoterol and oral corticosteroids, and that these improvements can be maintained for a year using budesonide and formoterol in the same inhaler.

Table 5.–The most frequently reported adverse events (AEs)

	B/F	B	F	Placebo
Subjects n	254	257	255	256
COPD[#]	48 (19)	62 (24)	73 (29)	79 (31)
Respiratory infection	36 (14)	34 (13)	33 (13)	24 (9)
Fever	5 (2)	9 (4)	11 (4)	2 (1)
Dyspnoea	5 (2)	5 (2)	12 (5)	5 (2)
Back pain	8 (3)	4 (2)	6 (2)	7 (3)
Pharyngitis	7 (3)	5 (2)	8 (3)	5 (2)
Chest pain	8 (3)	4 (2)	6 (2)	5 (2)
Hypertension	6 (2)	9 (4)	3 (1)	5 (2)
Pneumonia	8 (3)	5 (2)	7 (3)	2 (1)
Rhinitis	11 (4)	3 (1)	6 (2)	1 (<0.5)
Dysphonia	5 (2)	5 (2)	1 (<0.5)	1 (<0.5)
Moniliasis	4 (2)	4 (2)	2 (1)	0 (0)

Data are presented as n (%) of patients reporting at least one AE after the first dose of investigational product unless otherwise stated. B: budesonide; F: formoterol; COPD: chronic obstructive pulmonary disease. [#]: COPD was reported as an AE only if the COPD symptom (bronchitis, phlegm, cough, increased sputum production, breathlessness, wheeze, dyspnoea) was serious (resulted in death, was life-threatening, required hospitalisation or prolonged existing hospitalisation, or resulted in persistent or significant disability/incapacity), or resulted in the patient's withdrawal from the study.

This is the first study to show that after an intensification regimen, administration of an ICS and long-acting β_2-agonist in a single inhaler prolongs the time to a first COPD exacerbation, compared with monocomponents. Moreover, these data add further strong support to recent studies where these drug treatment classes have been combined and therapy has initially been withdrawn, rather than optimised, during the run-in phase [5, 6]. The exacerbation frequency in this study was almost identical to that reported in the previous study of budesonide/formoterol in COPD patients of a similar disease severity [5], and the effects of each treatment were the same in both studies. In this study, budesonide/formoterol was clearly better than monocomponents at preventing exacerbations, while budesonide had a small effect on episodes where oral corticosteroids were considered necessary. The lack of effect of formoterol may reflect the more severe nature of the episodes used as the outcome here (*i.e.* requiring medical intervention) rather than the "bad days" used as a surrogate for exacerbations in other studies [3]. The similarities of the data presented in this paper to those of SZAFRANSKI *et al.* [5] indicate that prior treatment optimisation does not influence this outcome. The more severe disease in the patients studied (FEV1 36% pred) is the likely explanation of the greater number of episodes seen here compared with other studies [6, 9], a difference that increases the power of the study to detect an effect of treatment. The 24% reduction in exacerbations with budesonide/formoterol compared with placebo may translate into worthwhile improvements in patient well-being. Furthermore, the reductions are probably underestimated since the lowest withdrawal rate occurred in the budesonide/formoterol group. It is likely that the most severely ill patients dropped out first, potentially leading to a lower number of exacerbations in the other groups. To some extent, this bias applies to lung function and HRQL differences as well.

Budesonide/formoterol was able to maintain FEV1 at the run-in level over the study year. In contrast, lung function (both FEV1 and PEF) returned to baseline by 1 month in patients treated with either placebo or budesonide and, as judged by the PEF data from the daily diary cards, this change occurred within 2 weeks of randomisation to these treatments. Numerically, the formoterol data lay between those of the other treatment limbs, but the values were significantly smaller than those measured using budesonide/formoterol. The size of the spirometric changes, comparing budesonide/formoterol with placebo and individual components, was almost identical to that seen when combination therapy was introduced after a period of treatment withdrawal [5, 6], rather than after the intensification regimen used here. The PEF data also show that within 2 weeks of stopping intensified therapy, clinical benefits of treatment optimisation were diminished in all patients not taking budesonide/formoterol.

Budesonide/formoterol produced significant improvements in daily symptom scores compared with placebo, as did formoterol *versus* placebo (except for cough, which was unchanged). The absolute changes were similar to those seen by SZAFRANSKI *et al.* [5] who used the same questionnaire. Even modest improvements in symptom scores are likely to lead to improved mobility and an increased level of activity. However, there were statistically and clinically significant differences between treatments in their ability to sustain the HRQL improvement after optimisation of therapy. Budesonide/formoterol treatment was associated with the largest difference in the SGRQ Total score compared with placebo, which clearly exceeded the minimum clinically important difference of 4 units [19]. Improvements in Total score compared with placebo were also clinically important with formoterol alone, and approached clinical relevance for budesonide alone. The additional effect of budesonide/formoterol on HRQL compared with monocomponents is likely to reflect the lower number of exacerbations experienced by these patients, since HRQL is known to be worse in frequent exacerbators [16].

All the active treatments had some positive effect on HRQL; the change seen over the year in the budesonide group being almost identical to that seen in the less spirometrically impaired Inhaled Steroids in Obstructive Lung Disease study patients, who were also studied after an initial course of prednisolone [9]. Inclusion of an optimised treatment phase may overcome problems in assessing HRQL in clinical studies as it reduces the immediate effect of withdrawing ICS that has been associated with more frequent exacerbations [23, 24]. This approach should permit a more realistic comparison to be made of treatment effect on HRQL and overcomes the "clinical-trial effect" seen in the placebo limb of other 1-yr trials [6].

In this study, AEs were monitored by specific enquiry at each visit. No new safety issues related to treatment with budesonide/formoterol were identified during 12-months treatment. The incidence of AEs related to COPD was clearly lower in the budesonide/formoterol group compared with the other groups, and overall, a low incidence of hoarseness and moniliasis was reported.

This study did not collect bone mineral density data, although the dose of budesonide used did not affect this variable during 3 yrs of treatment in patients with less advanced COPD [25]. As expected when studying a COPD population of this severity, a number of deaths occurred. The number of serious AEs and deaths reported were highest in the formoterol treatment group and most of these were events related to COPD. An investigation into the individual causes of death did not give an explanation for the apparent difference between the groups, and no increase in mortality during formoterol treatment without ICS was observed in a previous study with a similar patient population [5]. Conversely, increased disease severity/mortality has been reported in some recently published studies with bronchodilators alone [26–28]. These observations, together with the potential seriousness of severe exacerbations, suggest that a combination of a long-acting bronchodilator and an ICS may be particularly appropriate in patients with this severity of COPD.

The reasons for the improved efficacy of budesonide/formoterol are not yet clear, although corticosteroids can upregulate the number of β_2-receptors on the cell membrane and β_2-agonists may increase the nuclear localisation of glucocorticoid receptors [29]. It also seems that formoterol and budesonide in combination are more effective at reducing proliferation of airway smooth muscle than either drug alone, as a result of synchronised cellular signalling [30]. Clinically, each type of drug appears to add something to the combined effect with the improvement in symptoms, lung function (FEV1, PEF), and HRQL associated with formoterol being complemented by the reduction in exacerbations and better HRQL seen with budesonide. Whether these effects are merely additive or represent true synergy cannot be established here, but the difference in treatment withdrawal between the group taking budesonide/formoterol and those taking the other treatments is likely to be explained by these multiple beneficial actions.

This study has a number of implications. It provides further and clearer evidence of the effectiveness of ICS and long-acting β_2-agonists on health status, exacerbations, lung function (FEV1 and PEF) and HRQL, in COPD (GOLD stages III and IIV), and of their additional clinical benefit when combined in a single inhaler. Secondly, standardising therapy for a period before entry into a long clinical trial allowed greater improvements in HRQL than seen in similar trials that did not include this run-in treatment. This is a novel approach that may allow for easier interpretation of this endpoint, and merits further study.

Finally, this study provides evidence that intensifying treatment in stable chronic obstructive pulmonary disease may be a useful way of rapidly improving patient well-being and that this approach merits future study as an alternative to stepwise increments in treatment intensity.

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Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND

Long-acting beta-agonists and inhaled corticosteroids are used to treat chronic obstructive pulmonary disease (COPD), but their effect on survival is unknown.

METHODS

We conducted a randomized, double-blind trial comparing salmeterol at a dose of 50 μg plus fluticasone propionate at a dose of 500 μg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years. The primary outcome was death from any cause for the comparison between the combination regimen and placebo; the frequency of exacerbations, health status, and spirometric values were also assessed.

RESULTS

Of 6112 patients in the efficacy population, 875 died within 3 years after the start of the study treatment. All-cause mortality rates were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The hazard ratio for death in the combination-therapy group, as compared with the placebo group, was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P=0.052, adjusted for the interim analyses), corresponding to a difference of 2.6 percentage points or a reduction in the risk of death of 17.5%. The mortality rate for salmeterol alone or fluticasone propionate alone did not differ significantly from that for placebo. As compared with placebo, the combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85 and improved health status and spirometric values (P<0.001 for all comparisons with placebo). There was no difference in the incidence of ocular or bone side effects. The probability of having pneumonia reported as an adverse event was higher among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group and 18.3% in the fluticasone group) than in the placebo group (12.3%, P<0.001 for comparisons between these treatments and placebo).

CONCLUSIONS

The reduction in death from all causes among patients with COPD in the combination-therapy group did not reach the predetermined level of statistical significance. There were significant benefits in all other outcomes among these patients. (ClinicalTrials.gov number, NCT00268216.)

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*Committee members of the Towards a Revolution in COPD Health (TORCH) trial are listed in the Appendix.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a major cause of illness, death, and the use of health care resources globally.[1-3] The disease causes approximately 2.75 million deaths annually, and the number is projected to increase.[2] Treatment for COPD is focused on minimizing risk factors, improving symptoms, and preventing exacerbations.[3] With the exception of smoking-cessation programs for patients with early disease,[4] home oxygen treatment for persistent hypoxemia,[5,6] and lung-reduction surgery for selected patients with emphysema,[7] no treatment has been shown to reduce mortality.

Pulmonary inflammation is prominent in COPD.[8] Antiinflammatory drugs such as inhaled corticosteroids have little or no effect on the rate of decline of lung function[9,10] but may reduce the frequency of exacerbations,[9] especially when combined with an inhaled long-acting beta-agonist.[11] Retrospective analyses suggest that inhaled corticosteroids reduce the mortality rate among patients with COPD[12] and that adding a long-acting beta-agonist might increase this effect.[13] We hypothesized that the combination of the long-acting beta-agonist salmeterol and the inhaled corticosteroid fluticasone propionate would reduce mortality among patients with COPD, as compared with usual care. To test this hypothesis, we undertook the Towards a Revolution in COPD Health (TORCH) trial, a double-blind, placebo-controlled, randomized, parallel-group study comparing salmeterol plus fluticasone propionate (the combination regimen) with each of the components alone and with placebo over a 3-year period.

METHODS

Details of the study design and the analysis plan were published previously.[14] The complete study protocol is in Supplementary Appendix 1, available with the full text of this article at www.nejm.org.

PATIENTS

We recruited patients who were current or former smokers with at least a 10-pack-year history. Eligible patients were 40 to 80 years of age and had received a diagnosis of COPD, with a prebronchodilator forced expiratory volume in 1 second (FEV_1) of less than 60% of the predicted value,[15] an increase of FEV_1 with the use of 400 μg of albuterol of less than 10% of the predicted value for that patient, and a ratio of prebronchodilator FEV_1 to forced vital capacity (FVC) equal to or less than 0.70. For the exclusion criteria, see Table 1 in Supplementary Appendix 2. All patients gave written informed consent. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

STUDY DESIGN

This double-blind study was conducted at 444 centers in 42 countries; center and data auditing ensured the integrity of the data (see the study protocol in Supplementary Appendix 1). After a 2-week run-in period, eligible patients were randomly assigned, in permuted blocks with stratification according to country and smoking status, to treatment with the combination of salmeterol at a dose of 50 μg and fluticasone propionate at a dose of 500 μg (Advair Diskus, Seretide, GlaxoSmithKline) or salmeterol (Serevent, GlaxoSmithKline) alone at a dose of 50 μg, fluticasone propionate (Flovent Diskus, Flixotide, GlaxoSmithKline) alone at a dose of 500 μg, or placebo, all taken in the morning and the evening for 3 years. Study medications were administered as a dry powder with the use of an inhaler (Diskus, Accuhaler, GlaxoSmithKline). Inhalers were collected every 12 weeks, and the number of doses remaining in each inhaler was recorded to check adherence to the study regimen. Before the run-in period, all use of corticosteroids and inhaled long-acting bronchodilators was stopped, but patients could continue other medications for COPD.

After randomization, patients were seen every 12 weeks to confirm vital status, record any unscheduled visits to a health care provider, and note the occurrence of any adverse events. Postbronchodilator spirometry was performed and health status was assessed every 24 weeks. An independent safety and efficacy data monitoring committee performed safety reviews every 6 months, and two interim efficacy analyses were performed, the first after the first 358 deaths had occurred and the second after a total of 680 deaths had occurred.

OUTCOME MEASUREMENTS

Vital status was assessed until 3 years after treatment had begun, regardless of whether the patients continued to take study medication. The

primary end point was the time to death from any cause by 3 years. An independent clinical end point committee, whose members were unaware of the treatment assignments, determined the primary cause of death and whether death was related to COPD. The committee used information obtained from investigators, medical records, and other data, as available.

Secondary end points were the frequency of exacerbations, defined as a symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these, and health status, as assessed according to scores on the St. George's Respiratory Questionnaire.[16] Scores are based on a scale of 0 to 100, with lower scores indicating better functioning; a change of 4 units is generally considered clinically relevant. The questionnaire was administered in the 28 countries where a validated translation was available. Lung function was assessed with the use of postbronchodilator spirometry. For patients who withdrew from the study prematurely, all data on exacerbations, health status, and lung function available at the time of a patient's withdrawal from the study were included in the analysis.

SAFETY EVALUATION

Adverse events and medications were reviewed at each study visit. Additional information was collected about any fractures, classified as either traumatic or nontraumatic, with nontraumatic fractures considered to be caused by falls from less than standing height or falls occurring spontaneously. Dual-energy x-ray absorptiometry at the hip and lumbar spine and slit-lamp examinations were performed on patients' entry into the study and annually thereafter in a safety substudy conducted in the United States and involving 658 patients.

STATISTICAL ANALYSIS

All reported data analyses were prespecified. Assuming a 17% mortality rate in the placebo group at 3 years,[17] we estimated that 1510 patients would be needed for each study group to detect a reduction in mortality of 4.3 percentage points in the combination-therapy group, as compared with the placebo group (hazard ratio for death, 0.728), at a two-sided alpha level of 0.05 with 90% power. Two interim analyses of death from any cause were planned to assess whether there was overwhelming evidence of a benefit from the combination regimen, as compared with placebo, or of harm in any study group; these analyses were performed by the independent safety and efficacy data monitoring committee according to the method of Whitehead.[18] As a consequence, the P value for the primary comparison between the combination regimen and placebo was adjusted upward to conserve an overall significance level of 0.050.

The difference in times to death from any cause between the combination-therapy group and the placebo group was analyzed with the use of the log-rank test (with stratification according to smoking status) and expressed as a hazard ratio. We used a Cox proportional-hazards model as a supportive secondary analysis.

The frequency of exacerbations was analyzed with the use of a generalized linear model (assuming a negative binomial distribution, which accounts for variability among patients in the number and frequency of exacerbations), with the number of exacerbations as the outcome and the logarithm of time during which treatment was received as an offset variable. Total scores on the St. George's Respiratory Questionnaire and postbronchodilator FEV_1 were analyzed as changes from baseline values with the use of repeated-measures analysis of covariance (ANCOVA). Estimated differences between treatments at each visit were averaged with equal weights to determine the overall treatment effect during the 3-year study period. All efficacy analyses were performed according to the intention-to-treat principle. Comparisons other than those between the combination regimen and placebo and between the combination regimen and salmeterol alone were exploratory.

Times to the first fracture, eye disorder, and pneumonia were compared among the study groups in the safety population with the use of Kaplan–Meier estimates and the log-rank test, with stratification according to smoking status. In the safety substudy, bone mineral density for the total hip and lumbar spine was analyzed by repeated measures of ANCOVA, and the development of cataracts was analyzed with the use of logistic regression. (For details of the statistical analysis, see Supplementary Appendixes 1 and 2.)

The steering committee, made up of six academic investigators and two employees of the sponsor, developed the design and concept of the study, approved the statistical plan, had full access

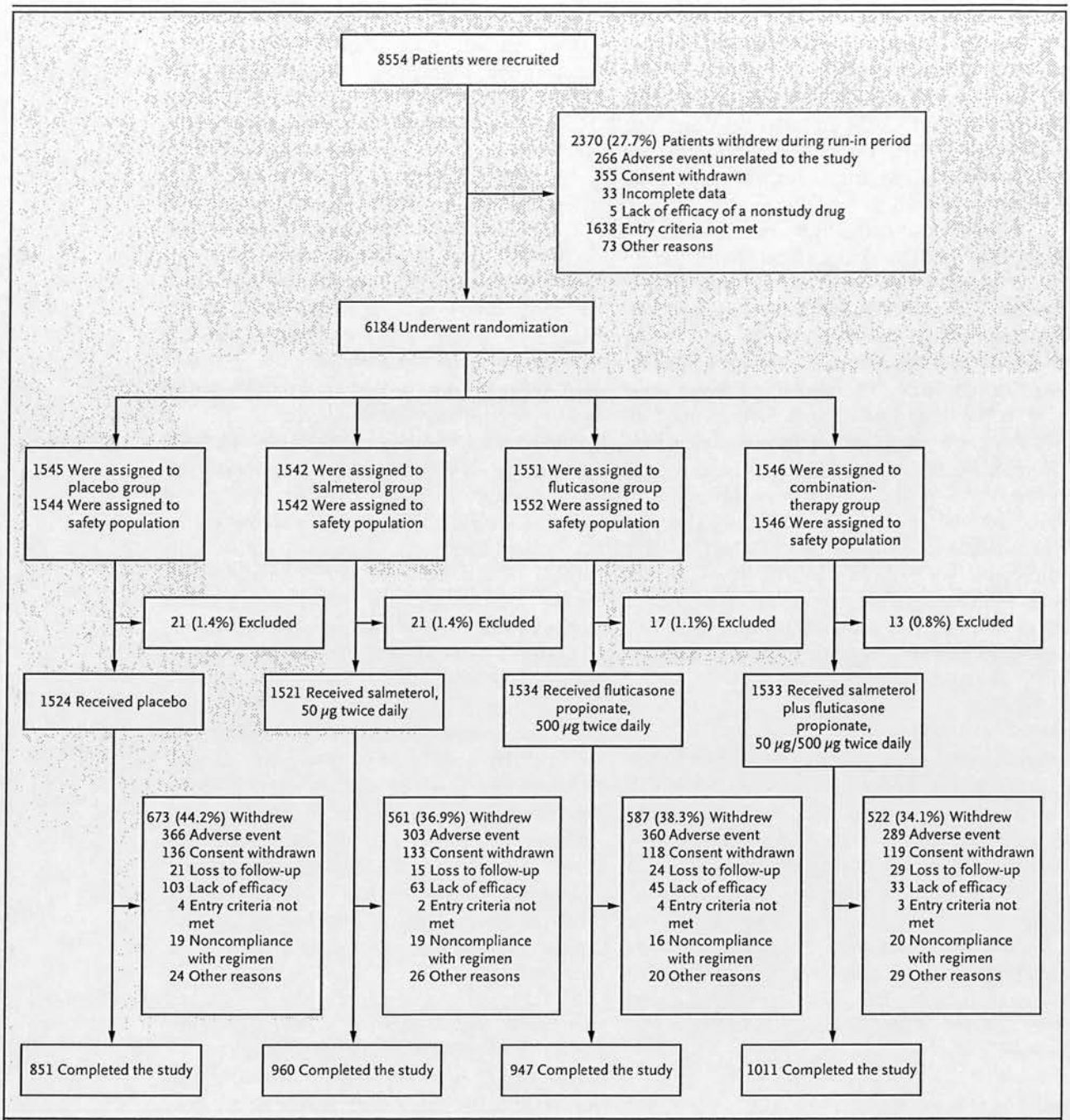

Figure 1. Enrollment of Patients and Completion of the Study.

Adverse events included death during the study period but may not have included deaths occurring after patients withdrew from the study. The number of patients who underwent randomization and the number of those included in the safety population differ in the placebo group and the fluticasone group, because one patient who was assigned to placebo received fluticasone propionate for more than half the study period; this patient was therefore included in the safety population of the fluticasone group and in the efficacy population of the placebo group. In each study group, patients were excluded from the efficacy analysis because during routine site visits and data audits, data from centers at which there were unacceptable research practices were excluded (see Supplementary Appendix 2). Vital status for patients included in the efficacy analysis was established at the end of the study, except for one patient in the combination-therapy group whose data were censored at the last point at which he was known to be alive (day 792).

Table 1. Demographic and Baseline Clinical Characteristics of Patients in the Efficacy Population.*

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)
Age at enrollment — yr	65.0±8.2	65.1±8.2	65.0±8.4	65.0±8.3
Male sex — no. (%)	1163 (76)	1160 (76)	1157 (75)	1151 (75)
Body-mass index†	25.4±5.2	25.4±5.2	25.4±5.1	25.4±5.3
Geographic region — no. (%)				
United States	345 (23)	346 (23)	348 (23)	349 (23)
Asia–Pacific	188 (12)	189 (12)	193 (13)	188 (12)
Eastern Europe	290 (19)	289 (19)	287 (19)	288 (19)
Western Europe	476 (31)	475 (31)	481 (31)	476 (31)
Other	225 (15)	222 (15)	225 (15)	232 (15)
Current smoker — no. (%)	658 (43)	651 (43)	661 (43)	660 (43)
Pack-years — no.	48.6±26.9	49.3±27.7	49.2±28.6	47.0±26.5
Previous treatment — no. (%)‡				
Inhaled corticosteroid	338 (22)	273 (18)	306 (20)	292 (19)
Long-acting beta-agonist	118 (8)	137 (9)	130 (8)	137 (9)
Inhaled corticosteroid plus long-acting beta-agonist	449 (29)	413 (27)	414 (27)	435 (28)
Exacerbation — no.‡				
Requiring antibiotics or oral corticosteroids	1.0±1.4	1.0±1.4	1.0±1.4	1.0±1.3
Requiring hospitalization	0.2±0.7	0.2±0.6	0.2±0.6	0.2±0.6
Lung function§				
Prebronchodilator FEV_1 — liters	1.12±0.40	1.10±0.39	1.12±0.39	1.12±0.40
Postbronchodilator FEV_1 — liters	1.22±0.42	1.21±0.41	1.22±0.41	1.22±0.42
FEV_1 — % of predicted	44.1±12.3	43.6±12.6	44.1±12.3	44.3±12.3
Reversibility — % of predicted FEV_1¶	3.7±3.7	3.7±3.9	3.7±3.7	3.6±3.6
Prebronchodilator FEV_1:FVC (%)	48.6±10.9	48.7±10.8	48.5±10.7	48.7±10.8
Total score at baseline on St. George's Respiratory Questionnaire‖	49.0±17.4	49.9±16.6	49.5±17.1	48.9±17.4

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Exacerbations during the 12 months before screening were self-reported.
§ Clinical data are from visit 1 (the screening visit). FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.
¶ Reversibility denotes the change in the FEV_1 after the administration of 400 μg of albuterol to less than 10% of the predicted value for the patient.
‖ Scores on the St. George's Respiratory Questionnaire are based on a scale of 0 to 100, with lower scores indicating better functioning; a change of 4 units is considered clinically relevant. Data are given for the centers at which the questionnaire was administered.

to and interpreted the data, wrote the manuscript, and was responsible for the decision to publish the manuscript. An academic author wrote a draft of the manuscript; an employee of the sponsor performed the statistical analysis. The academic authors vouch for the veracity and completeness of the data and the data analysis. The sponsor did not place any restrictions on the academic authors regarding statements made in the final manuscript.

RESULTS

STUDY POPULATION

Of 8554 patients recruited, 6184 underwent randomization (Fig. 1). Of these, 72 patients at five

sites were excluded from the efficacy analysis because these sites failed to meet the standards of the study for Good Clinical Practice and ethical practices and were closed before the study ended (see Supplementary Appendix 2). These 72 patients were included in the safety analysis, and a total of 6112 patients were included in the efficacy population.

Demographic and baseline clinical characteristics of the efficacy population are shown in Table 1. The mean age was 65 years, and the mean value of postbronchodilator FEV_1 was 44% of the predicted value. During the year before entry into the study, more than half the patients had used inhaled corticosteroids, a long-acting beta-agonist, or both, and 57% of the patients had reported an exacerbation. The proportion of patients who withdrew from the study was significantly higher in the placebo group (44%) than in the three other groups, and the proportion was lowest in the combination-therapy group (34%) (Fig. 2A). The total number of years of exposure to the study drugs was 3678 in the combination-therapy group, 3238 in the placebo group, 3499 in the salmeterol group, and 3532 in the fluticasone group. The rate of adherence to treatment was similar in all groups, ranging from 88% to 89% of the prescribed doses taken.

Figure 2 (facing page). Outcomes.

In the combination regimen, salmeterol was administered at a dose of 50 μg and fluticasone propionate at a dose of 500 μg twice daily. Salmeterol alone was administered at a dose of 50 μg twice daily, and fluticasone propionate alone was administered at a dose of 500 μg twice daily. Cumulative incidences of discontinuation of a study drug at 3 years were 43.5% in the placebo group, 36.4% in the salmeterol group, 38.1% in the fluticasone group, and 33.7% in the group receiving the combination of salmeterol plus fluticasone propionate (Panel A). Intergroup comparisons yielded the following hazard ratios for the discontinuation of a study medication: 0.69 (95% CI, 0.62 to 0.78, P<0.001) for the combination-therapy group versus the placebo group; 0.89 (95% CI, 0.79 to 0.999; P<0.05) for the combination-therapy group versus the salmeterol group; 0.86 (95% CI, 0.76 to 0.96; P=0.010) for the combination-therapy group versus the fluticasone group; 0.78 (95% CI, 0.70 to 0.86; P<0.001) for the salmeterol group versus the placebo group; and 0.81 (95% CI, 0.72 to 0.90; P<0.001) for the fluticasone group versus the placebo group. Patients discontinuing a study medication were included in the mortality analysis at 3 years but could receive any treatment. In the analysis for the primary end point of the probability of death from any cause at 3 years, the risk of death in the placebo group was 15.2%, as compared with 12.6% in the combination-therapy group. Salmeterol and fluticasone propionate in combination reduced the risk of death at any time during the 3-year study period by 17.5% (P=0.052) (Panel B). The probability of COPD-related death at 3 years was 6.0% in the placebo group, 6.1% in the salmeterol group, 6.9% in the fluticasone group, and 4.7% in the combination-therapy group (Panel C). The effect of each study medication on health status (assessed according to changes in patients' total scores on the St. George's Respiratory Questionnaire) and FEV_1 during the 3-year study period are shown in Panels D and E, respectively. Values in the tables below the graphs represent the numbers of patients alive (Panel B), the numbers of of patients alive or dead from non–COPD-related causes (Panel C), or the number of patients remaining in the study (Panels A, D, and E). I bars represent standard errors (at approximately 1, 2, and 3 years in Panels A, B, and C). HR denotes hazard ratio.

MORTALITY

Vital status was known at 3 years for 6111 of the 6112 patients included in the efficacy population. There were 875 deaths within 3 years after randomization. The proportions of deaths from any cause at 3 years were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The absolute risk reduction for death in the combination-therapy group as compared with the placebo group was 2.6%, and the hazard ratio was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P=0.052), corresponding to a reduction in the risk of death at any time in the 3 years of 17.5% (95% CI, −0.2 to 31.9) (all adjusted for the interim analyses) (Fig. 2B and Table 2).

Prespecified secondary analyses for mortality were also performed: Cox proportional-hazards testing yielded a hazard ratio of 0.811 (95% CI, 0.670 to 0.982; P=0.03) (Table 2); log-rank testing, stratified according to smoking status and country of residence, yielded a hazard ratio of 0.815 (95% CI, 0.673 to 0.987; P=0.04) (see Table 2 in Supplementary Appendix 2). There was no interaction between treatment and age, sex, region of country, baseline FEV_1 categorized by disease stage according to the Global Initiative for Chronic Obstructive Lung Disease, body-mass index, or smoking status. Adjusting for exposure to smoking (pack-years) did not affect the results.

The risk of death in the salmeterol group and in the fluticasone group did not differ significantly from that in the placebo group (Table 2). The risk was similar among patients who died

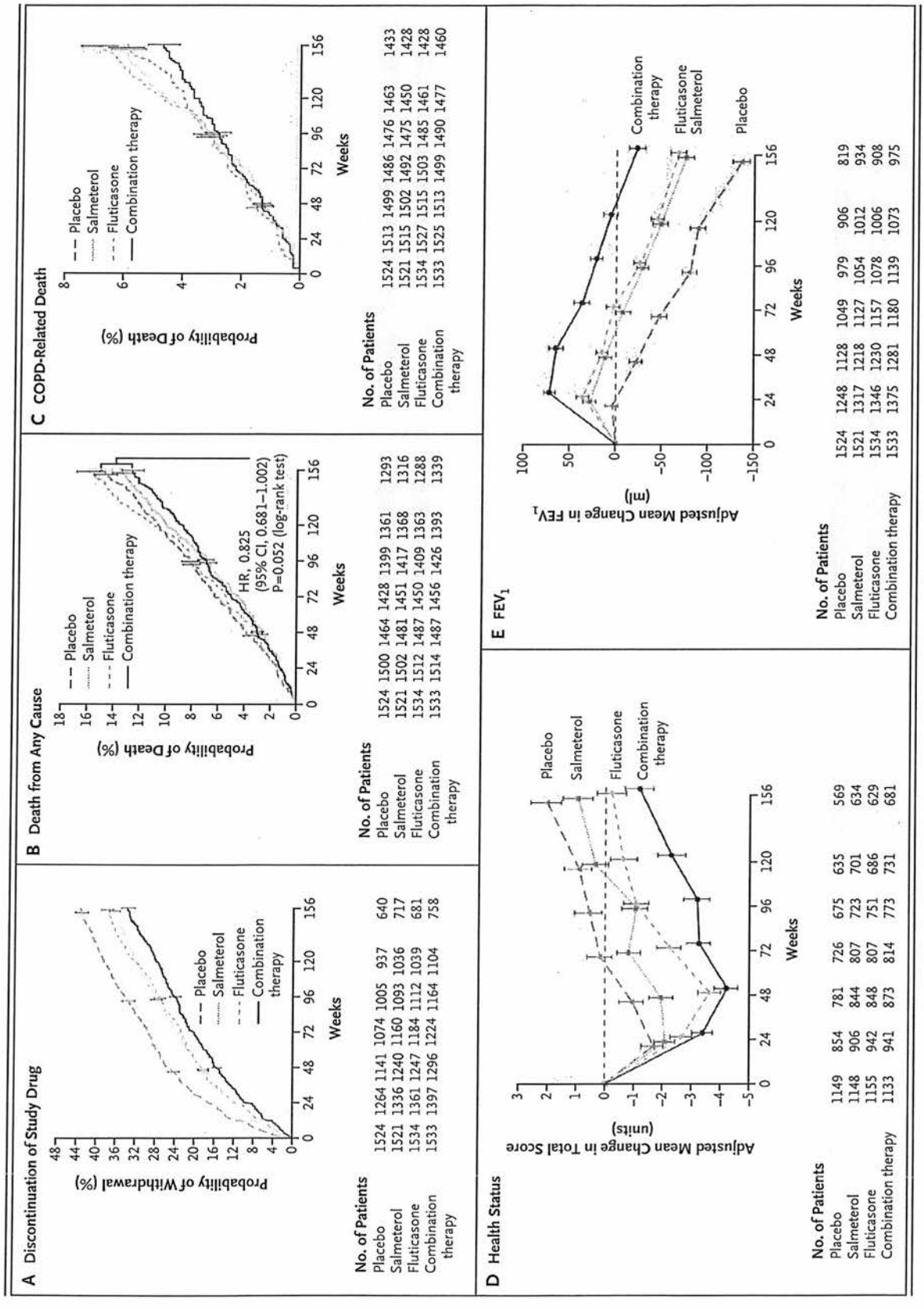

Table 2. Results of the Mortality Analysis and the Efficacy Analysis for Exacerbation.

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)	Comparison	Hazard Ratio (95% CI)	P Value
Mortality analysis							
No. of deaths from any cause	231	205	246	193			
Probability of death at 3 yr — %	15.2	13.5	16.0	12.6	Combination therapy vs. placebo (adjusted)*	0.825 (0.681–1.002)	0.052
					Combination therapy vs. placebo (unadjusted)	0.820 (0.677–0.993)	0.04
					Combination therapy vs. salmeterol	0.932 (0.765–1.134)	0.48
					Combination therapy vs. fluticasone propionate	0.774 (0.641–0.934)	0.007
					Salmeterol vs. placebo	0.879 (0.729–1.061)	0.18
					Fluticasone propionate vs. placebo	1.060 (0.886–1.268)	0.53
Adjusted probability of death at 3 yr — %†	12.6	10.9	13.3	10.3	Combination therapy vs. placebo	0.811 (0.670–0.982)	0.03
					Combination therapy vs. salmeterol	0.946 (0.777–1.151)	0.58
					Combination therapy vs. fluticasone propionate	0.768 (0.636–0.927)	0.006
					Salmeterol vs. placebo	0.857 (0.710–1.035)	0.11
					Fluticasone propionate vs. placebo	1.056 (0.883–1.264)	0.55
COPD-related deaths‡							
No. of deaths	91	93	106	72			
Probability of death at 3 yr — %	6.0	6.1	6.9	4.7	Combination therapy vs. placebo	0.78 (0.57–1.06)	0.11
					Combination therapy vs. salmeterol	0.77 (0.56–1.04)	0.09
					Combination therapy vs. fluticasone propionate	0.67 (0.50–0.90)	0.008
					Salmeterol vs. placebo	1.01 (0.76–1.35)	0.93
					Fluticasone propionate vs. placebo	1.16 (0.88–1.53)	0.30

Primary cause of death up to 3 yr — no. (%)							
Cardiovascular	71 (5)	45 (3)	61 (4)	60 (4)			
Pulmonary	74 (5)	80 (5)	91 (6)	61 (4)			
Cancer	45 (3)	44 (3)	51 (3)	44 (3)			
Other	23 (2)	22 (1)	30 (2)	11 (1)			
Unknown	18 (1)	14 (1)	13 (1)	17 (1)			
Efficacy analysis for exacerbation							
						Rate Ratio (95% CI)	
Annual rate							
Moderate or severe	1.13	0.97	0.93	0.85	Combination therapy vs. placebo	0.75 (0.69–0.81)	<0.001
					Combination therapy vs. salmeterol	0.88 (0.81–0.95)	0.002
					Combination therapy vs. fluticasone propionate	0.91 (0.84–0.99)	0.02
					Salmeterol vs. placebo	0.85 (0.78–0.93)	<0.001
					Fluticasone propionate vs. placebo	0.82 (0.76–0.89)	<0.001
Requiring systemic corticosteroids	0.80	0.64	0.52	0.46	Combination therapy vs. placebo	0.57 (0.51–0.64)	<0.001
					Combination therapy vs. salmeterol	0.71 (0.63–0.79)	<0.001
					Combination therapy vs. fluticasone propionate	0.87 (0.78–0.98)	0.02
					Salmeterol vs. placebo	0.80 (0.72–0.90)	<0.001
					Fluticasone propionate vs. placebo	0.65 (0.58–0.73)	<0.001
Severe (requiring hospitalization)	0.19	0.16	0.17	0.16	Combination therapy vs. placebo	0.83 (0.71–0.98)	0.03
					Combination therapy vs. salmeterol	1.02 (0.87–1.20)	0.79
					Combination therapy vs. fluticasone propionate	0.95 (0.82–1.12)	0.56
					Salmeterol vs. placebo	0.82 (0.69–0.96)	0.02
					Fluticasone propionate vs. placebo	0.88 (0.74–1.03)	0.10

* Only the primary comparison was adjusted because interim analyses were performed. Unadjusted data for the primary end point are provided for comparison.
† The adjusted probability of death was calculated with the use of a Cox proportional-hazards model.
‡ Cause of death was adjudicated by the clinical end-point committee.

while receiving a study medication (data not shown) and those who died from COPD-related causes (Fig. 2C). The risk of death in the combination-therapy group did not differ significantly from that in the salmeterol group, but patients receiving the combination regimen were less likely to die than those receiving fluticasone propionate (hazard ratio for death, 0.774 [95% CI, 0.641 to 0.934]; P=0.007). Overall, 27% of the deaths were adjudicated as due to cardiovascular causes, 35% to pulmonary causes, and 21% to cancer (for other causes of death, see Table 3 in Supplementary Appendix 2).

EXACERBATIONS, HEALTH STATUS, AND LUNG FUNCTION

According to our statistical models, the annual rate of exacerbations was 0.85 (95% CI, 0.80 to 0.90) in the combination-therapy group and 1.13 (95% CI, 1.07 to 1.20) in the placebo group, resulting in a rate ratio for exacerbations of 0.75 (95% CI, 0.69 to 0.81; P<0.001), which is a reduction of 25% and corresponds to a number needed to treat of four to prevent one exacerbation in 1 year. Annual rates of exacerbations in the salmeterol group and the fluticasone group were significantly lower than in the placebo group (Table 2). Overall, 26% of the patients were hospitalized at least once during the 3-year study period. Annual admission rates were 17% lower in the combination-therapy and salmeterol groups than in the placebo group (P≤0.03) (Table 2), corresponding to a number needed to treat of 32 to prevent one hospitalization in 1 year.

Total scores on the St. George's Respiratory Questionnaire initially improved from baseline in all groups, with the greatest changes occurring in the combination-therapy group (mean score at baseline, 48.7, with a mean reduction of 3.0 units averaged over 3 years), as compared with the placebo group (a mean score of 48.4 at baseline, with an increase of 0.2 unit in the placebo group) (Fig. 2D and Table 3). Similarly, for lung function, the mean baseline FEV_1 in the combination-therapy group was 1.236 liters with an average increase of 0.029 liter, whereas in the placebo group, the mean baseline FEV_1 was 1.257 liters and a decrease of 0.062 liter. Averaged over 3 years, the health status (a reduction of 3.1 units in the score for the St. George's Respiratory Questionnaire) and spirometric measurements (an increase in FEV_1 of 0.092 liter) in the combination-therapy group were significantly better than in the groups receiving placebo, salmeterol alone, or fluticasone propionate alone (Fig. 2E and Table 3).

ADVERSE EVENTS AND SAFETY

Adverse events were reported by 90% of the patients in the study, and serious adverse events were reported by 41% of the patients (Table 4). (For mortality data for the safety population, see Fig. 1 and Table 4 in Supplementary Appendix 2.) The most frequently reported adverse event was an exacerbation of COPD. The probability of having pneumonia reported as an adverse event during the 3-year study period was significantly greater among patients receiving a study medication containing fluticasone propionate: the probability was 19.6% in the combination-therapy group, 12.3% in the placebo group, 13.3% in the salmeterol group, and 18.3% in the fluticasone group (P<0.001 for the comparison between both the combination-therapy and fluticasone groups and the placebo group). Among patients receiving study medications, there were 8 deaths from pneumonia in the combination-therapy group, 7 in the placebo group, 9 in the salmeterol group, and 13 in the fluticasone group. There was no significant difference in the probability of fractures among the groups (6.3% in the combination-therapy group, 5.1% in the placebo group, 5.1% in the salmeterol group, and 5.4% in the fluticasone group). There was no excess of cardiac disorders among patients treated with the combination regimen or salmeterol alone (reported event rates per study year, 0.087 in the combination-therapy group, 0.113 in the placebo group, 0.114 in the salmeterol group, and 0.102 in the fluticasone group). In the safety substudy, there were no significant differences in bone mineral density or in the numbers of patients in whom cataracts developed between the groups receiving active study drugs and the placebo group (Table 4).

DISCUSSION

In this trial, the reduction in mortality from any cause in the combination-therapy group, as compared with the placebo group, did not meet the predetermined level of statistical significance. During the 3 years of the study, treatment with the combination regimen resulted in significantly fewer exacerbations and improved health status and lung function, as compared with placebo.

Table 3. Other Efficacy Outcomes.*

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)	Comparison	Difference (95% CI)	P Value
St. George's Respiratory Questionnaire*							
No. of patients completing a validated questionnaire	1231	1232	1248	1240			
No. of patients included in the analysis†	924	980	1005	1002			
Mean baseline score	48.4	49.4	49.5	48.7			
Adjusted mean change in score averaged over 3 yr (units)	+0.2	−0.8	−1.8	−3.0	Combination therapy vs. placebo	−3.1 (−4.1 to −2.1)	<0.001
					Combination therapy vs. salmeterol	−2.2 (−3.1 to −1.2)	<0.001
					Combination therapy vs. fluticasone propionate	−1.2 (−2.1 to −0.2)	0.02
					Salmeterol vs. placebo	−1.0 (−2.0 to 0)	0.06
					Fluticasone propionate vs. placebo	−2.0 (−2.9 to −1.0)	<0.001
Postbronchodilator FEV_1							
No. of patients included in the analysis†	1261	1334	1356	1392			
Mean baseline FEV_1 (liters)‡	1.26	1.23	1.23	1.24			
Adjusted mean change in FEV_1 averaged over 3 yr (liters)	−0.062	−0.021	−0.015	+0.029	Combination therapy vs. placebo	0.092 (0.075 to 0.108)	<0.001
					Combination therapy vs. salmeterol	0.050 (0.034 to 0.067)	<0.001
					Combination therapy vs. fluticasone propionate	0.044 (0.028 to 0.061)	<0.001
					Salmeterol vs. placebo	0.042 (0.025 to 0.058)	<0.001
					Fluticasone propionate vs. placebo	0.047 (0.031 to 0.064)	<0.001

* Scores on the St. George's Respiratory Questionnaire are based on a scale of 0 to 100, with lower scores indicating better functioning; a change of 4 units is generally considered clinically relevant.
† Patients for whom at least one measurement was obtained after baseline were included in the analysis.
‡ Patients included in the analysis were those for whom data on the change from baseline FEV_1 were available.

There are two possible reasons why the reduction in mortality in the combination-therapy group, as compared with the placebo group, did not achieve statistical significance. The first is that there is no effect of salmeterol plus fluticasone propionate on survival. In this scenario, the data would suggest that the observed symptomatic and functional improvement derives from mechanisms other than those that prolong life. It could be that mortality is influenced mainly by factors that are currently unidentified and unresponsive to therapy with salmeterol plus fluticasone propionate.

The second possible reason, which we believe is the more likely one, is that salmeterol plus fluticasone propionate does have an effect on mortality but that our study was underpowered to detect this effect. Our power calculations were based on the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, and there were fewer deaths in the placebo group than anticipated.[14,17] The TORCH study was designed to have 90% power to detect an effect of 4.3 percentage points on overall mortality; in practice, we identified a reduction of 2.6 percentage points. In addition, there was a high withdrawal rate, which was highest among patients in the placebo group, who were free to receive active therapy subsequently. Furthermore, performing the second interim analysis so close to the final analysis increased the threshold required for significance. More studies are needed to determine whether either of these explanations or another explanation accounts for the primary finding.

Our data on the secondary outcomes are consistent with and extend previous observations in studies using combinations of inhaled corticosteroids and long-acting beta-agonists[19-21] in showing that the combination regimen reduced exacerbations significantly, as compared with placebo, including those exacerbations requiring hospitalization. The combination regimen was also significantly better than each of its components alone in preventing exacerbations, and these benefits were accompanied by sustained improvements in health status and FEV_1; the values for both were better at the end of the trial than at baseline. Unlike previous studies in which reductions in exacerbations and improvements in health status have also been reported,[19,21] in our study there was no requirement of exacerbations during the year before entry into the trial. Furthermore, the greater number of patients withdrawing from the placebo group is likely to have resulted in an underestimation of the effect of the combination regimen on all the secondary outcomes. Nevertheless, the number needed to treat to prevent an exacerbation in 1 year was 4, and the number needed to treat to prevent a hospitalization was 32.

An important safety finding, identified because the size of the study was sufficient to detect infrequent events, was the excess of patients who received a diagnosis of pneumonia among those receiving study medications containing fluticasone propionate. This finding had not been previously reported in studies involving the use of inhaled corticosteroids by patients with COPD. Since the finding was unexpected, there was no prospective definition of pneumonia in the study protocol (e.g., confirmation on chest radiography). However, this finding was observed in the different subgroups, which suggests that it may be an important signal whose mechanism is currently unclear and requires further study. The increase in pneumonia did not appear to represent an increase in the number of deaths. As determined by the independent clinical end-point committee, among deaths attributed to pneumonia in patients in the safety population while they were receiving a study medication, there was one more death in the combination-therapy group and six more in the fluticasone group than in the placebo group.

The increase in oropharyngeal side effects among patients receiving fluticasone propionate or the combination regimen was expected, but there was no evidence of excess cardiac events among those receiving salmeterol alone or the combination regimen. The total number of fractures, including those associated with minimal trauma or none, did not differ significantly among the four groups. This finding was in keeping with the absence of a significant difference among the groups in bone mineral density among patients in the U.S. substudy. The prevalence of cataracts at baseline in all the study groups was high, but it was not influenced by treatment during the course of the study. However, exposure to the study medications for 3 years may not be long enough to detect differences in the occurrence of fractures and eye disorders.

The TORCH study recruited patients with COPD from around the world, and we think that our findings can therefore be generalized. The par-

Table 4. Adverse Events among 6184 Patients in the Safety Population and 658 Patients in the Substudy of Bone Mineral Density.

Adverse Event	Placebo Group (N=1544)	Salmeterol Group (N=1542)	Fluticasone Group (N=1552)	Combination-Therapy Group (N=1546)
Reported during treatment — % of patients				
Any event	90	90	90	89
Serious event	41	40	42	43
Drug-related event	13	12	19	18
Event resulting in withdrawal or discontinuation of study medication	24	20	23	18
Total exposure to study medication — yr	3278	3531	3555	3700
Most commonly reported event during treatment — rate per yr				
COPD exacerbation	0.92	0.76	0.78	0.67
Upper respiratory tract infection	0.10	0.08	0.09	0.11
Nasopharyngitis	0.09	0.09	0.10	0.10
Pneumonia	0.04	0.04	0.07	0.07
Bronchitis	0.05	0.05	0.05	0.05
Headache	0.08	0.06	0.06	0.05
Back pain	0.04	0.04	0.04	0.04
Sinusitis	0.03	0.03	0.04	0.04
Cough	0.03	0.03	0.04	0.03
Hypertension	0.03	0.03	0.03	0.02
Additional events associated with the use of corticosteroids — rate per yr				
Candidiasis	0.02	0.02	0.09	0.07
Dysphonia	0.004	0.005	0.017	0.028
Of specific interest during treatment — % of patients*				
Pneumonia	12.3	13.3	18.3†	19.6‡
Fractures				
Total	5.1	5.1	5.4	6.3
Nontraumatic	1.8	2.5	1.7	1.7
Eye disorders	3.6	4.3	4.1	5.2
Safety substudy				
Cataracts§				
None at baseline — no. of patients/total no.	47/164	41/166	47/163	52/165
Developed during treatment — no. of patients/total no. (%)	10/47 (21)	6/41 (15)	8/47 (17)	14/52 (27)
Bone mineral density¶				
Hip — no. of patients/total no.	52/164	78/166	65/163	82/165
Change from baseline — %‖	−3.1	−1.7	−2.9	−3.2
Lumbar spine — no. of patients/total no.	50/164	76/166	63/163	81/165
Change from baseline — %‖	0	1.5	−0.3	−0.3

* Probability was calculated by the Kaplan–Meier method.
† P<0.001 for the comparison between the fluticasone group and the placebo group.
‡ P<0.001 for the comparisons between the group receiving salmeterol plus fluticasone propionate and the placebo group and between the combination-therapy group and the salmeterol group.
§ Patients who had cataracts at baseline were not included in the subsequent analysis.
¶ Patients included in the analysis were those for whom measurements of bone mineral density at baseline and at 158 weeks were available.
‖ The percentage of change was calculated as [(ratio of bone mineral density at week 158 to the value at baseline) − 1] multiplied by 100.

ticular strengths of the study are the virtually complete survival data to 3 years and the independent adjudication of causes of death, which eliminated between-country variation in death certification. Although the TORCH study is a large COPD trial, as compared with studies of mortality associated with other major chronic illnesses such as cardiovascular disease,[22-24] its size is modest. The results of our mortality analysis should be viewed in this context. The potential for a reduction in the risk of death of 2.6 percentage points among patients treated with salmeterol plus fluticasone propionate, as compared with placebo, and the 17.5% reduction in the risk of death that was identified in the study clearly merit further investigation in future large, prospective trials. Until such trials are completed, our data support the use of salmeterol plus fluticasone propionate in the clinical management of COPD.

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This study is dedicated to the memory of Professor Romain Pauwels, who played a major role in planning the TORCH investigation and led the investigators until his untimely death.

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APPENDIX

For a complete list of investigators of the Towards a Revolution in COPD Health (TORCH) study, see Supplementary Appendix 2. Committee members were as follows: **Steering Committee:** P.M.A. Calverley (chair), Liverpool, United Kingdom; J.A. Anderson, Greenford, United Kingdom; B. Celli, Boston; G.T. Ferguson, Livonia, MI; C. Jenkins, Sydney; P.W. Jones, London; K. Knobil, J.C. Yates, Research Triangle Park, NC; J. Vestbo, Manchester, United Kingdom. **Safety and Efficacy Data Monitoring Committee:** R. Cherniack, Denver; T. Similowski, Paris; J. Cleland, Hull, United Kingdom; A. Whitehead, Reading, United Kingdom. **Clinical End Point Committee:** R. Wise, Baltimore; L. McGarvey, Belfast, Northern Ireland; M. John, Berlin.

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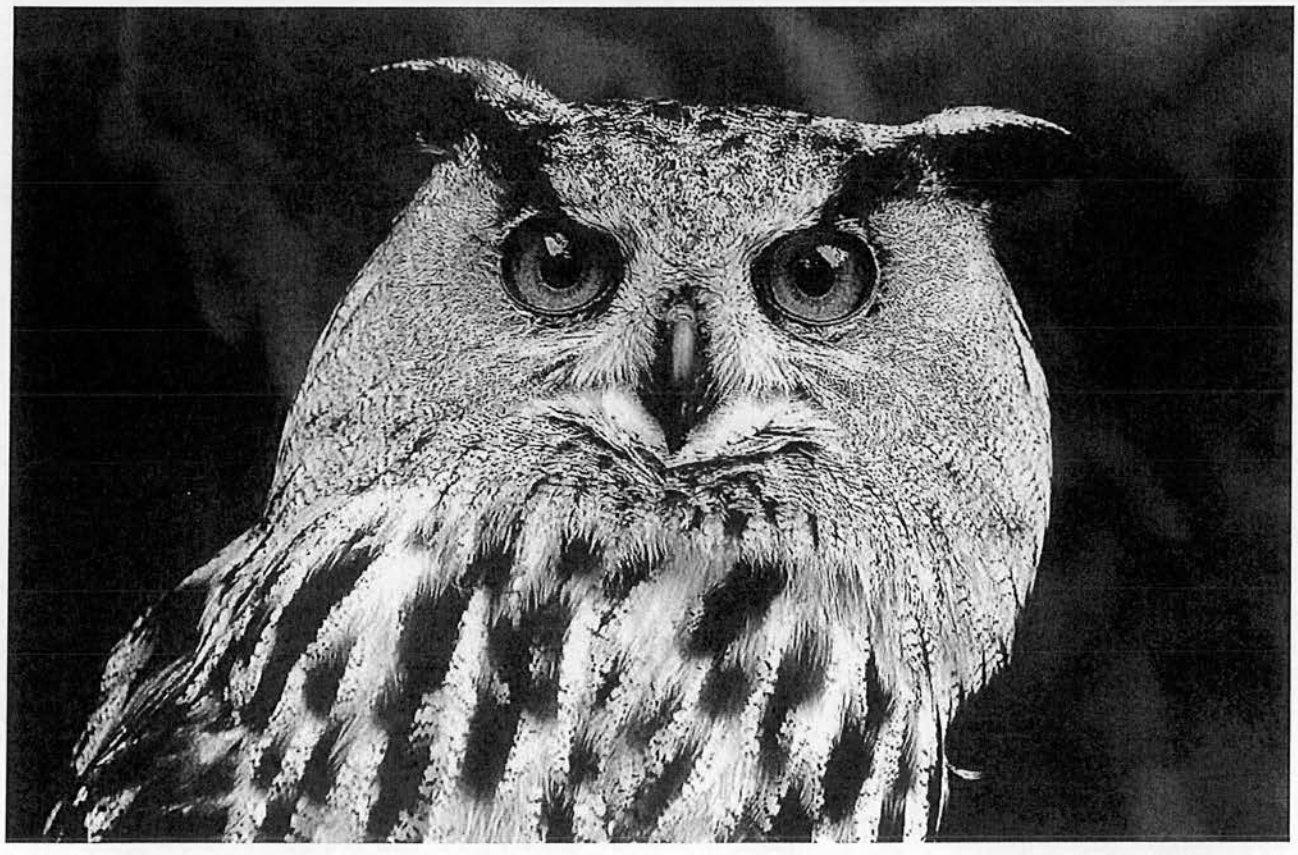

Eagle Owl

Ira Kirschenbaum, M.D.

AA

Effect of Pharmacotherapy on Rate of Decline of Lung Function in Chronic Obstructive Pulmonary Disease

Results from the TORCH Study

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Rationale: **Chronic obstructive pulmonary disease (COPD) is characterized by an accelerated decline in lung function. No drug has been shown conclusively to reduce this decline.**

Objectives: **In a *post hoc* analysis of the Toward a Revolution in COPD Health (TORCH) study, we investigated the effects of combined salmeterol 50 μg plus fluticasone propionate 500 μg, either component alone or placebo, on the rate of post-bronchodilator FEV_1 decline in patients with moderate or severe COPD.**

Methods: **A randomized, double-blind, placebo-controlled study was conducted from September 2000 to November 2005 in 42 countries. Of 6,112 patients from the efficacy population, 5,343 were included in this analysis.**

Measurements and Main Results: **Spirometry was measured every 24 weeks for 3 years. There were 26,539 on-treatment observations. The adjusted rate of decline in FEV_1 was 55 ml/year for placebo, 42 ml/year for salmeterol, 42 ml/year for fluticasone propionate, and 39 ml/year for salmeterol plus fluticasone propionate. Salmeterol plus fluticasone propionate reduced the rate of FEV_1 decline by 16 ml/year compared with placebo (95% confidence interval [CI], 7–25; $P < 0.001$). The difference was smaller for fluticasone propionate and salmeterol compared with placebo (13 ml/year; 95% CI, 5–22; $P = 0.003$). Rates of decline were similar among the active treatment arms. FEV_1 declined faster in current smokers and patients with a lower body mass index, and varied between world regions. Patients who exacerbated more frequently had a faster FEV_1 decline.**

Conclusions: **Pharmacotherapy with salmeterol plus fluticasone propionate, or the components, reduces the rate of decline of FEV_1 in patients with moderate-to-severe COPD, thus slowing disease progression.**

Clinical trial (GSK Study Code SCO30003) registered with www.clinicaltrials.gov (NCT00268216).

Keywords: FEV_1; salmeterol; fluticasone propionate; disease progression

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The decline in FEV_1 has been accepted as a key marker for progression of chronic obstructive pulmonary disease (COPD). To date, smoking cessation is the only intervention that has conclusively been shown to alter the rate of decline in FEV_1.

What This Study Adds to the Field

This study shows that pharmacotherapy with combined salmeterol 50 μg plus fluticasone propionate 500 μg, or either component alone, can reduce the rate of decline of FEV_1 in patients with moderate-to-severe COPD, thus slowing disease progression.

Chronic obstructive pulmonary disease (COPD), a major cause of morbidity worldwide (1), is characterized by airflow obstruction, as determined by the ratio of the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Disease progression has been assessed using the rate of FEV_1 decline, which is greater than normal in COPD (2, 3). To date, smoking cessation is the only intervention that has conclusively been shown to alter the rate of decline in FEV_1 (4).

While the pathogenesis of COPD is complex, studies suggest that airway inflammation plays an important role in disease progression (3, 5, 6). The intensity of inflammation relates to the degree of airflow obstruction (5), and may result from oxidant-induced damage. However, neither the antioxidant drug N-acetyl cysteine nor the nonspecific antiinflammatory effects of inhaled corticosteroids have been shown to modify the rate of decline in FEV_1 (7–11). Meta-analyses of the inhaled corticosteroid (ICS) studies have yielded conflicting results (12–14). Salmeterol and other long-acting β-agonists are highly selective bronchodilators that have been shown to improve lung function, dyspnea, and health status in relatively short-term studies (15, 16). However, their possible long-term effect on rate of decline in FEV_1 has never been evaluated. It has recently been shown that the administration of an ICS combined with a long-acting β-agonist modifies the expression of inflammation in mucosal biopsies and sputum of patients with COPD (6), raising the possibility that this pharmacologic combination could have an effect on the rate of decline of lung function.

The Toward a Revolution in COPD Health (TORCH) study investigated the effect of salmeterol/fluticasone propionate (SFC) and either component alone compared with placebo on mortality, as well as the impact on the rate of exacerbations, health-related quality of life, and postbronchodilator FEV_1. The primary efficacy analysis has already been published (17). The

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original report concentrated on the effect of therapy on mortality as the primary outcome, and presented the mean effect on lung function over 3 years as a supportive analysis, without addressing the change in the rate of FEV_1 decline, a variable that has been accepted as a reasonable surrogate marker for disease progression.

Before treatment unblinding, we decided to test the hypothesis that pharmacotherapy would modify the rate of decline of postbronchodilator FEV_1, compared with placebo. We also conducted an exploratory analysis of the factors that could affect FEV_1 rate of decline, since an association has been reported between frequency of exacerbation and an increased rate of decline of FEV_1 (18, 19). Some of these results have been previously reported in the form of an abstract (20).

METHODS

Design Overview

Details of the TORCH study design have been published elsewhere (17, 21). TORCH was a multi-center, randomized, double-blind, parallel-group, placebo-controlled study. All corticosteroids and inhaled long-acting bronchodilators were stopped before the run-in period, but other COPD medications were allowed. After a 2-week run-in period, eligible patients were stratified by smoking status and randomized to receive either SFC 50/500 μg, salmeterol (SAL) 50 μg, fluticasone propionate (FP) 500 μg, or placebo twice daily for 3 years via a Diskus/Accuhaler inhaler (GlaxoSmithKline, Greenford, UK) (*see* online supplement).

The primary efficacy endpoint of TORCH was all-cause mortality at 3 years. Other efficacy endpoints included rate of exacerbations (*see* online supplement), health status, and post-bronchodilator spirometry every 24 weeks.

Setting and Participants

Details of the study settings and patient inclusion and exclusion criteria have been published previously (17). All patients gave informed consent and the study was approved by ethical review boards and conducted in accordance with the Declaration of Helsinki. For this analysis we included all patients with a baseline and at least one on-treatment FEV_1.

Randomization and Interventions

Full details of the randomization procedure have been reported previously (17, 21).

Outcomes and Follow-up

In this report, the primary outcome was the rate of post-bronchodilator FEV_1 decline. At visit 1 (start of the 2-wk run-in period), the highest of three acceptable measurements of FEV_1 was recorded before, and 30 minutes after, inhalation of 400 μg albuterol as recommended by the ATS (22). Reversibility was calculated as a percentage of the predicted normal FEV_1 (23). Patients refrained from using short-acting bronchodilators for at least 6 hours, and long-acting β_2 agonists (LABA) for at least 12 hours, before visit 1. At visit 2 (baseline) and every 24 weeks thereafter, post-bronchodilator measurements of FEV_1 were obtained (before which subjects were not required to withhold their COPD medication).

Spirometers were regularly calibrated according to manufacturer recommendations and a calibration log was kept. Lung function data were reviewed centrally during the study and queried if values differed significantly in consecutive visits (criteria used for the query are published in the online supplement). After completion of the study, the variability of the spirometric values was assessed by analyzing the variance of individual regression slopes and comparing them with those obtained in the ISOLDE trial (11), in which spirometric measurements were the primary endpoint and were closely monitored.

Statistical Analysis

The study was powered on the primary endpoint of all-cause mortality, as described previously (17, 21), and was not formally powered for the analysis of rate of decline in FEV_1.

The effect of treatment on rate of decline of absolute FEV_1, percentage change in a year and as percentage of predicted FEV_1 was analyzed using a random coefficients model, including terms for treatment, time on treatment in years, treatment by time interaction, and covariates of smoking status, sex, age, baseline FEV_1, region (*see* Table 2 footnote for countries included in each region), and body mass index (BMI). This methodology was the same as that used in other landmark studies, which assessed rate of decline in lung function in COPD (9–11). To derive the percentage change in a year, the logarithm of FEV_1 was analyzed. To eliminate immediate improvements, the decline was evaluated from 24 weeks onward (the time at which the first on-treatment measurement was made). The effects of covariates on the rate of FEV_1 decline were investigated using this model as exploratory analyses, including the covariate by time interaction individually for smoking status, sex, age, baseline percentage predicted FEV_1, region, ethnic origin, BMI, previous exacerbation history, and baseline St George's Respiratory Questionnaire (SGRQ). We also tested whether the treatment effect on the rate of decline was consistent for subgroups by including a treatment-by-covariate-by-time interaction individually in this model.

A further analysis was performed by calculating individual patient slopes from the regression analysis of each subject's FEV_1 values and applying ANCOVA to these slopes. At least two on-treatment FEV_1 measurements were required for this analysis.

In addition, we report exploratory summary statistics of individual patient slopes categorized by number of exacerbations reported during the study, and by whether subjects survived or died during the 3 years of the study. All analyses were performed on an intention-to-treat basis

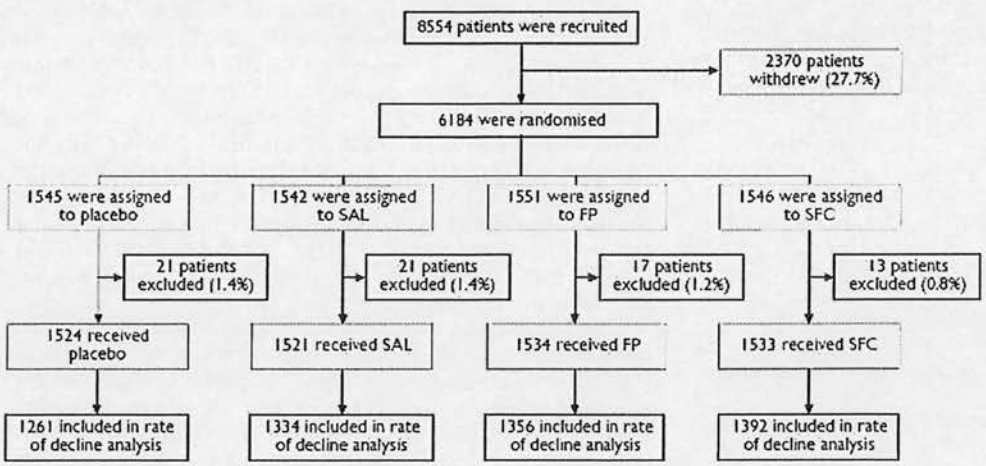


Figure 1. Modified patient disposition diagram and analyses populations, based on full CONSORT diagram published in the study by Calverley and coworkers (17). FP = fluticasone propionate; SAL = salmeterol; SFC = salmeterol/fluticasone propionate combination. Modified by permission from Reference 17.

TABLE 1. BASELINE* CHARACTERISTICS OF SUBJECTS WITH AT LEAST ONE ON-TREATMENT FEV_1, INCLUDED IN THE ANALYSIS OF FEV_1 DECLINE

Characteristic	Placebo (n = 1,261)	SAL (n = 1,334)	FP (n = 1,356)	SFC (n = 1,392)
Mean age (SD), yr	64.8 (8.2)	64.9 (8.2)	64.9 (8.4)	64.9 (8.3)
Male, n (%)	976 (77)	1,029 (77)	1,026 (76)	1,049 (75)
Mean body mass index (SD), kg/m²	25.5 (5.2)	25.4 (5.2)	25.3 (5.0)	25.4 (5.3)
Current smoker, n (%)	563 (45)	600 (45)	596 (44)	601 (43)
Baseline post-bronchodilator FEV_1 (SD), ml	1,257 (444)	1,231 (431)	1,233 (437)	1,236 (455)
% predicted post-bronchodilator FEV, (SD) ml	45.0 (13.0)	44.3 (13.3)	44.8 (13.3)	44.7 (13.4)
Region, n (%)				
United States	271 (21)	290 (22)	299 (22)	312 (22)
Asia Pacific	170 (13)	175 (13)	177 (13)	175 (13)
Eastern Europe	257 (20)	270 (20)	270 (20)	273 (20)
Western Europe	387 (31)	410 (31)	412 (30)	433 (31)
Other	176 (14)	189 (14)	198 (15)	199 (14)

Definition of abbreviations: CI = confidence interval; FP = fluticasone propionate; SAL = salmeterol; SFC = salmeterol/fluticasone propionate combination.

* Baseline was at randomization visit.

using SAS software version 8.2 (SAS Institute, Inc., Cary, NC) on a Unix platform. For the principal analyses, a threshold for statistical significance was set at 0.05. For the effect of covariates on the slopes, which were exploratory analyses, the threshold was set at 0.10.

Role of the Funding Source

Funding for the TORCH study was provided by GlaxoSmithKline. The TORCH Steering Committee, comprising six academics and three representatives of the sponsor, developed the design and concept, approved the statistical plan, had full access to and interpreted the data, wrote the manuscript, and was responsible for decisions with regard to publication.

RESULTS

Patients

A total of 6,112 patients composed the efficacy population of TORCH. Of these, 5,343 (87%) had at least one on-treatment FEV_1 and were included in the decline analysis (Figure 1). The characteristics of these patients at baseline are shown in Table 1. The number of patients was smaller in the placebo compared with the active treatment arms because more patients withdrew within the first 24 weeks from the placebo arm (17% in placebo compared with 12% in the SAL and FP arms, and 9% in the combination arm). During the study, 187 (3%) patients took tiotropium while on study medication (44 [3%] placebo, 62 [4%] SAL, 40 [3%] FP, and 41 [3%] SFC).

Rate of Decline of FEV_1

A total of 26,539 on-treatment observations were available for the analysis. The maximum number of on-treatment measurements a patient could contribute to the estimation of the rate of FEV_1 decline was 6, and 64% of patients contributed this number. The average number of measurements was 5, with only 19% of patients having 3 or fewer, primarily due to early withdrawal or death. In the placebo arm, patients withdrawing before the end of the study had a faster rate of decline (76 ml/year) compared with those completing the trial (54 ml/year).

The rate of absolute decline of FEV_1 for each arm is summarized in Table 2, and that of % predicted FEV_1 is shown in Table 3. Figure 2 shows the adjusted means and standard errors at each visit and fitted lines from the random coefficients model of FEV_1. The rate of decline of FEV_1 was slowest in patients on SFC and fastest in those randomized to the placebo arm. From Week 24 onwards, the adjusted rate of decline in FEV_1 was 39 ml/year for SFC, 42 ml/year for both SAL and FP and 55 ml/year for placebo, a reduction of 16 ml/year with SFC compared with placebo ($P < 0.001$), and 13 ml versus placebo for both FP and SAL ($P = 0.003$) (Figure 2). These treatment differences remained when the values were expressed as % predicted FEV_1 (Table 3) or as percentage of the baseline value (where the rate of decline was 3%/yr for SFC, 4%/yr for SAL and FP, and 5%/yr for placebo). In addition, the analysis of individual regression slopes produced similar findings. The standard deviations of individual regression slopes were similar in all treatment groups ranging from 160 to 180 ml/year. These values are similar to those observed in the ISOLDE trial (166 ml/yr for FP and 187 ml/yr for placebo).

Effect of Covariates on FEV_1 Slopes of Rate of Decline

A slower rate of decline in absolute ml/year was observed in former smokers, females, patients 65 years and older, and those with FEV_1 less than 30% predicted. Patients with a BMI greater

TABLE 2. ADJUSTED YEARLY RATE OF DECLINE IN FEV_1 BY TREATMENT GROUP

	Placebo (n = 1,261)	SAL (n = 1,334)	FP (n = 1,356)	SFC (n = 1,392)
Adjusted rate of decline (SE), ml/yr	−55.3 (3.2)	−42.3 (3.1)	−42.3 (3.1)	−39.0 (3.0)
Active treatment minus placebo (SE), ml/yr	–	13.0 (4.4)	13.0 (4.4)	16.3 (4.4)
95% CI	–	4.3, 21.7	4.3, 21.7	7.7, 24.9
P value	–	0.003	0.003	< 0.001
SFC minus components (SE), ml/yr	–	3.3 (4.3)	3.3 (4.3)	–
95% CI	–	−5.1, 11.7	−5.1, 11.6	–
P value	–	0.441	0.445	–

Definition of abbreviations: CI = confidence interval; FP = fluticasone propionate; SAL = salmeterol; SFC = salmeterol/fluticasone propionate combination.

Random coefficients model including smoking status, sex, age, baseline FEV_1, region, body mass index (BMI), treatment, time, and treatment by time.

TABLE 3. ADJUSTED YEARLY RATE OF DECLINE IN % PREDICTED FEV_1 BY TREATMENT GROUP

	Placebo (n = 1,261)	SAL (n = 1,334)	FP (n = 1,356)	SFC (n = 1,392)
Adjusted rate of decline (SE), %/yr	−1.5 (0.1)	−1.0 (0.1)	−1.1 (0.1)	−0.9 (0.1)
Active treatment minus placebo (SE), %/yr	–	0.5 (0.2)	0.4 (0.2)	0.6 (0.2)
95% CI	–	0.2, 0.8	0.1, 0.8	0.3, 0.9
P value	–	0.002	0.006	< 0.001
SFC minus components (SE),%/yr	–	0.1 (0.2)	0.1 (0.2)	–
95% CI	–	−0.2, 0.4	−0.2, 0.4	–
P value	–	0.627	0.401	–

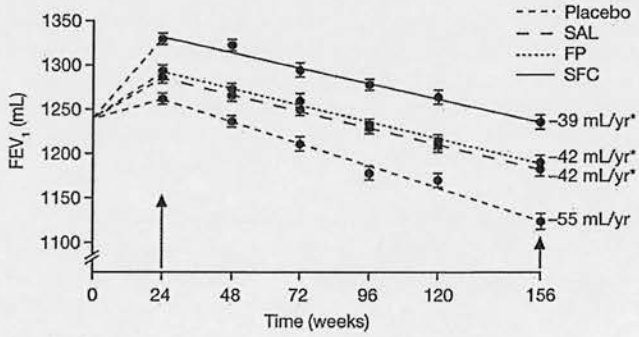
For definition of abbreviations, *see* Table 3.

Random coefficients model including smoking status, sex, age, baseline % predicted FEV_1, region, body mass index (BMI), treatment, time, and treatment by time.

than or equal to 25 showed a slower decline in lung function (Table 4).The rate of decline in patients from the Asia Pacific and Eastern Europe regions was slower than that of patients from the other regional groups. These relationships were preserved when the rate of FEV_1 decline was expressed as a percentage change in a year for all of these covariates except sex, where there was no difference, and in patients with FEV_1 less than 30% predicted (*see* Table E1 in the online supplement). In this group of patients, the FEV_1 declined by 28 ml/year, compared with 47ml/year for the other patients (Table 4), but when this change was expressed as a percentage of baseline (4%/yr) it was within the range of the other groups (4.4%/yr and 3.3%/yr for 30–49% and ≥ 50% predicted FEV_1, respectively; Table E1).

The effect of treatment on FEV_1 decline was similar irrespective of smoking status, sex, age, baseline FEV_1, region of the world, ethnicity, BMI, previous exacerbations, and baseline SGRQ. The differences between placebo and the treatment arms were unaffected by whether the patients had taken ICS or LABA in the 12 months before the study (Tables E2 and E3).

We observed no association between previous exacerbation history based on patient recall and FEV_1 decline (Table 4). However, there appeared to be an association between number of exacerbations documented during the duration of the study and the rate of decline of FEV_1 (*see* Table 5), with higher rates of decline being evident in patients experiencing more exacerbations.



No. of patients

Placebo	1261	1248	1128	1049	979	906	819
SAL	1334	1317	1218	1127	1054	1012	934
FP	1356	1346	1230	1157	1078	1006	908
SFC	1392	1375	1281	1180	1139	1073	975

Figure 2. Adjusted means at each visit and rate of decline (ml/yr) in post-bronchodilator FEV_1 by treatment (random coefficients model). The slope over time was calculated from Week 24 to Week 156, as indicated by the *arrows*, and was significantly steeper in the patients receiving placebo versus those receiving active therapies. FP = fluticasone propionate; SAL = salmeterol; SFC = salmeterol/fluticasone propionate combination. *$P \leq 0.003$ compared with placebo. Note: *Vertical bars* represent standard errors of the adjusted means at each visit. The number of patients at each clinic visit with FEV_1 measurements is shown below the graph.

DISCUSSION

COPD is characterized by airflow obstruction, which is usually progressive (2, 3), and hence, the measured decline in FEV_1 has been accepted as a key marker for disease progression and a target for therapeutic trials. The longitudinal analysis of lung function from the TORCH data set presented here is the first to identify significant reductions in FEV_1 decline in those patients receiving active treatment.

The normal rate of FEV_1 decline in healthy subjects is approximately 30 ml/year (24, 25). The modeled rate of decline in post-bronchodilator FEV_1 in patients receiving placebo in TORCH was 55 ml/year; similar to that seen in the Lung Health Study 1 (–52 ml) (26), Lung Health Study 2 (–47 ml) (10), BRONCUS (–54 ml) (7), and ISOLDE studies (–59 ml) (11), and slightly lower than in EUROSCOP (–69 ml) (9), where the baseline FEV_1 was higher and all randomized subjects were current smokers. We identified a significantly lower rate of decline in FEV_1 (by 13–16 ml/yr) in those patients receiving active therapy. Rate of decline was similar among the three active treatment arms of the study. Although treatment did not abolish the accelerated decline in lung function, it did ameliorate it substantially, decreasing the excess FEV_1 decline attributable to historically obtained values in patients with COPD (27).

All three treatments showed improvements in post-bronchodilator FEV_1 relative to placebo at each visit, but the mechanism responsible for the effect on rate of decline is not clear, as all treatments have potentially significant nonbronchodilator effects (6, 28, 29). Whether the maintenance of airway patency and reduction in hyperinflation, improvements in mucociliary clearance, or decreases in airway inflammation contribute singly or together to produce the observed functional change cannot be determined in TORCH, and further mechanistic studies are needed. The results of the forthcoming UPLIFT trial, where a long-acting bronchodilator drug tiotropium is compared with placebo with lung function decline as its primary outcome, may help clarify mechanisms, since tiotropium is a bronchodilator without primary antiinflammatory action (30, 31).

In the TORCH trial, there were significant reductions in exacerbations in all treatment arms, with the greatest reductions observed with the SFC combination (17). This is consistent with our data, in which treatment decreased the rate of decline in FEV_1 and this effect was greatest in patients receiving SFC. There was an association between exacerbation frequency documented during the study and FEV_1 decline, supporting previous observations (18, 19) (Table 5). However, in patients who had no exacerbations during the study, the rate of decline

TABLE 4. EFFECT OF BASELINE COVARIATES ON FEV_1 SLOPES (ml/YR)

	Number of Subjects in Analysis	Baseline Mean FEV_1 (SD), ml	Adjusted Rate of FEV_1 Decline (SE), ml/yr	Effect of Covariates on Slopes
Smoking status				$P < 0.001$
Current (n = 2,630)	2,360	1,300 (457)	−55.0 (2.3)	
Former (n = 3,482)	2,983	1,191 (424)	−36.6 (2.1)	
Sex				$P = 0.027$
Female (n = 1,481)	1,263	1,019 (339)	−38.5 (3.2)	
Male (n = 4,631)	4,080	1,307 (448)	−46.6 (1.8)	
Age, yr				$P < 0.001$
< 55 (n = 701)	633	1,473 (542)	−51.7 (4.3)	
55–64 (n = 1,972)	1,746	1,284 (455)	−51.3 (2.6)	
65–74 (n = 2,670)	2,323	1,172 (391)	−39.5 (2.4)	
⩾ 75 (n = 769)	641	1,125 (360)	−36.7 (4.7)	
% Predicted FEV_1				$P < 0.001$
< 30 (n = 937)	778	711 (160)	−28.4 (4.3)	
30–49 (n = 3,019)	2,630	1,114 (264)	−47.2 (2.2)	
⩾ 50 (n = 2,156)	1,935	1,620 (395)	−47.0 (2.5)	
Region				$P < 0.001$
United States (n = 1,388)	1,172	1,205 (451)	−49.4 (3.4)	
Asia Pacific (n = 758)	697	1,045 (400)	−30.7 (4.2)	
Eastern Europe (n = 1,154)	1,070	1,341 (435)	−38.2 (3.3)	
Western Europe (n = 1,908)	1,642	1,307 (423)	−50.9 (2.8)	
Other (n = 904)	762	1,178 (441)	−48.4 (4.2)	
Ethnic Origin				$P < 0.001$
White (n = 5,006)	4,338	1,278 (439)	−48.1 (1.7)	
Black (n = 95)	83	1,139 (429)	−43.4 (13.1)	
Asian (n = 769)	705	1,046 (400)	−30.6 (4.2)	
American Hispanic (n = 193)	173	1,107 (468)	−22.4 (8.4)	
Other (n = 49)	44	1,121 (333)	−46.8 (17.4)	
BMI				$P < 0.001$
< 20 (n = 824)	719	1,024 (393)	−51.1 (4.4)	
20 to < 25 (n = 2,301)	2,003	1,195 (427)	−50.5 (2.5)	
25 to < 29 (n = 1,642)	1,424	1,316 (440)	−42.1 (2.9)	
⩾ 29 (n = 1,345)	1,197	1,351 (358)	−35.1 (3.2)	
Exacerbations in the year before study				$P = 0.800$
0 (n = 2,626)	2,314	1,282 (439)	−45.8 (2.3)	
1 (n = 1,513)	1,340	1,244 (447)	−44.5 (3.1)	
⩾ 2 (n = 1,973)	1,689	1,176 (435)	−43.4 (2.8)	
Baseline SGRQ Total Score				$P = 0.122$
< 38 (n = 1,427)	1,140	1,381 (431)	−43.0 (3.3)	
38 to < 50 (n = 1,276)	992	1,251 (418)	−42.0 (3.6)	
50 to < 62 (n = 1,135)	964	1,180 (430)	−53.0 (3.7)	
⩾ 62 (n = 1,120)	966	1,144 (426)	−47.5 (3.9)	

Definition of abbreviations: BMI = body mass index; SGRQ = St George's Respiratory Questionnaire.

Random coefficients model including smoking status, gender, age, baseline FEV_1, region, body mass index (BMI), prior exacerbations, treatment, time and treatment by time, and covariate by time (the term for covariate by time was added one at a time to the multivariate model including all the covariates).

was significantly faster in the placebo group compared with active treatments (56 ml/yr versus 27–31 ml/yr), which suggests that the effect of treatment on exacerbations was not the sole mechanism responsible for the reduced rate of decline with active treatment.

Our results confirm those of previous studies, which have shown that smoking status, age, and baseline percent predicted FEV_1 affect the rate of lung function decline (32). However, our data extend these observations in the Lung Health Study population to patients with more severe COPD. In addition, we have identified two novel factors associated with FEV_1 decline, specifically BMI and region of origin, although these could also be due to differences in height. Together with already known variables such as baseline lung function, smoking status, and exacerbation frequency, they may help explain between-subject differences in FEV_1 decline. Lung function declined

TABLE 5. SUMMARY OF INDIVIDUAL FEV_1 REGRESSION SLOPES BY EXACERBATION RATE

	Placebo (n = 1,137)			SAL (n = 1,232)			FP 500 (n = 1,242)			SFC (n = 1,292)			Total (n = 4,903)		
	N	Mean Slope	SD	n	Mean Slope	SD	n	Mean Slope	SD	n	Mean Slope	SD	n	Mean Slope	SD
Moderate/severe exacerbation (rate per annum)															
0	294	−55.6	184.7	341	−29.3	192.9	309	−30.7	208.2	362	−26.9	225.4	1,306	−34.9	204.4
> 0 to 1.0	421	−59.1	144.9	475	−43.2	128.5	467	−47.8	122.7	499	−42.2	135.4	1,862	−47.7	132.9
> 1.0	422	−64.2	213.8	416	−55.3	164.7	466	−52.6	155.4	431	−58.8	170.2	1,735	−57.6	176.8

Definition of abbreviations: FP = fluticasone propionate; SAL = salmeterol; SFC = salmeterol/fluticasone propionate combination.

least (35 ml/yr) in patients with a BMI of 29 or higher, was higher in patients with BMI between 25 and 29 (42 ml/yr), but was greatest in patients with a baseline BMI below 25 (51 ml/yr). This suggests an important association between systemic consequences of the disease and disease progression in the lungs (33, 34), but does not necessarily indicate causality. Interestingly, patients from the Asia Pacific and Eastern Europe regions, as well as patients of Asian and American Hispanic ethnic origins, had a slower rate of decline compared with Western Europeans and North Americans, even when expressed as percentage change in FEV_1. This may be related to the fact that patients in Asia Pacific and Eastern Europe had lower mean FEV_1 absolute and percent predicted at baseline (Table E4), thus providing less capacity for FEV_1 to decline over time. Alternatively, other factors yet unexplored such as genetic, socioeconomic, or environmental differences may be important.

Female patients lost FEV_1 at a slower rate than that of male patients, a result similar to that reported in the long-term follow-up of the Lung Health Study (4). Women who quit smoking in that study lost an average of 22 ml/year, compared with men who lost an average of 30 ml/year. In the smokers, the values were 54 and 66 ml/year, respectively. In this TORCH dataset, women lost 39 ml/year, whereas men lost 47 ml/year irrespective of smoking status. This difference disappeared when the rate of decline was expressed as a percentage change in a year, with women losing 4.2% versus 3.9% per year for men. These results suggest that the sex difference was related to airway size rather than intrinsic biologic differences in the progression of COPD.

There were some limitations to our study. As in other long-term COPD trials (35, 36), many patients failed to complete the study, with significantly more withdrawing from the placebo limb. Moreover, those withdrawing showed more rapid deterioration in lung function, a finding noted by others (37). This preferential dropout in the placebo arm of those patients whose function worsens more rapidly (evidenced by the greater decline in patients who withdrew early compared with those who completed) actually minimizes the differences observed in rate of FEV_1 decline. In addition, the random coefficients model (11) gives most weight to patients who complete the trial, and hence, the differences in lung function decline we report may be conservative estimates of the true treatment effect. We are confident that our principal findings are reliable, since they were consistent whether expressed in ml/year or as percentage change per year. It has been suggested that changing the usual therapy of the patient with COPD can influence the results of interventional studies (38). This was not the case in TORCH, where prior therapy with ICS or LABA was unrelated to the beneficial effect of therapy on the rate of FEV_1 decline.

Another limitation of the study was that the FEV_1 was not a primary outcome in this mortality trial. However, postbronchodilator lung function was extensively measured, and the more than 26,000 spirometric assessments obtained over the 3 years of the study provided a unique opportunity to evaluate how lung function evolved in patients randomized to different treatments.

A theoretical limitation was the less rigorous monitoring of spirometry compared with other trials primarily evaluating lung function decline. However, the standard deviation of our FEV_1 measurements was comparable with that in previous studies, in which spirometry was performed more frequently and using more rigorous quality control (10, 11). These data suggest that measuring postbronchodilator spirometry in a larger number of patients, as in TORCH, compensated for any inherent between-tests variability in FEV_1.

In summary, we have shown for the first time that pharmacologic therapy slows the decline in lung function in patients with COPD. Given the progressive nature of COPD, halving of the excess decline in FEV_1 is likely to be clinically important in patients such as those who participated in TORCH.

Conflict of Interest Statement: B.R.C. has been reimbursed by GlaxoSmithKline (GSK), Boehringer Ingelheim (BI), AstraZeneca (AZ), and Almirall for participating in advisory boards and for lectures. N.E.T. is an employee of GSK and holds stock options with GSK. J.A.A. is an employee of GSK and holds stock options with GSK. G.T.F. in the last 3 years has participated as a speaker in scientific meetings or courses organized and financed by GSK, BI, and Pfizer; served on advisory boards for GSK, BI, Novartis, and Schering Plough; served as a consultant to GSK and Novartis; received an investigator initiated research grant from GSK; and has participated in multi-center clinical trials for GSK, BI, Novartis, Emphasys, Dey, Forest, and Altana. C.R.J. has been reimbursed by GSK, AZ, Novartis, and BI for participating on advisory boards and speaking at educational symposia. The studies she has managed have received research funding paid to the Woolcock Institute of Medical Research from GSK and AZ. P.W.J. has received consultancy fees averaging $10,000 over 3 years (2004–2007), $14,000 in lecture fees in 2006, and a grant of $190,000 in 2004, all from GSK. J.V. has been reimbursed by GSK for presenting of various meetings, receiving fees of $14,000 in 2004, $12,000 in 2005, and $12,000 in 2006. J.V. received $450,000 in 2006 and expects to receive $400,000 per year as research grants for participating in multi- and single-center clinical studies sponsored by GSK. J.V.'s wife is an employee of AZ Denmark; neither J.V. nor his wife owns shares in any pharmaceutical company. K.K. is an employee of the sponsor of the study (GSK) and owns shares of GSK. J.C.Y. is an employee of GSK and owns shares in GSK. P.M.A.C. has acted as a study leader for investigations sponsored by GSK, Altana, and Chiesi; has served on advisory boards supported by GSK, Pfizer, and AZ; and his department has received research funding from GSK to conduct non–product-related research.

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TORCH Steering Committee members: P.M.A. Calverley (Chairman), Liverpool, UK; J.A. Anderson, Greenford, UK; B. Celli, Boston, MA; G.T. Ferguson, Livonia, MI; C.R. Jenkins, Sydney, Australia; P.W. Jones, London, UK; K. Knobil, Research Triangle Park, USA; J. Vestbo, Manchester, UK; J.C. Yates, Research Triangle Park, NC.

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Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

Peter M A Calverley, Klaus F Rabe*, Udo-Michael Goehring, Søren Kristiansen, Leonardo M Fabbri†, Fernando J Martinez†, for the M2-124 and M2-125 study groups‡*

Summary

Background The phosphodiesterase-4 inhibitor roflumilast can improve lung function and prevent exacerbations in certain patients with chronic obstructive pulmonary disease (COPD). We therefore investigated whether roflumilast would reduce the frequency of exacerbations requiring corticosteroids in patients with COPD.

Methods In two placebo-controlled, double-blind, multicentre trials (M2-124 and M2-125) with identical design that were done in two different populations in an outpatient setting, patients with COPD older than 40 years, with severe airflow limitation, bronchitic symptoms, and a history of exacerbations were randomly assigned to oral roflumilast (500 µg once per day) or placebo for 52 weeks. Primary endpoints were change in prebronchodilator forced expiratory volume in 1 s (FEV_1) and the rate of exacerbations that were moderate (glucocorticosteroid-treated) or severe. Analysis was by intention to treat. The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.

Findings Patients were assigned to treatment, stratified according to smoking status and treatment with longacting β_2 agonists, and given roflumilast (n=1537) or placebo (n=1554). In both studies, the prespecified primary endpoints were achieved and were similar in magnitude. In a pooled analysis, prebronchodilator FEV_1 increased by 48 mL with roflumilast compared with placebo ($p<0\cdot0001$). The rate of exacerbations that were moderate or severe per patient per year was 1·14 with roflumilast and 1·37 with placebo (reduction 17% [95% CI 8–25], $p<0\cdot0003$). Adverse events were more common with roflumilast (1040 [67%]) than with placebo (963 [62%]); 219 (14%) patients in the roflumilast group and 177 (12%) in the placebo group discontinued because of adverse events. In the pooled analysis, the difference in weight change during the study between the roflumilast and placebo groups was –2·17 kg.

Interpretation Since different subsets of patients exist within the broad spectrum of COPD, targeted specific therapies could improve disease management. This possibility should be explored further in prospective studies.

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Introduction

Chronic obstructive pulmonary disease (COPD) is increasing in prevalence; it is associated with periodic exacerbations, resulting in patient anxiety,[1] worsening health status, lung function decline, and increase in mortality rate.[2–4] Effective management involves pharmacological and non-pharmacological treatments.[5] Longacting inhaled bronchodilator drugs (β_2 agonists and anticholinergic drugs) can improve health status and reduce the frequency of exacerbations, effects that are greater when longacting β_2 agonists are used in combination with inhaled corticosteroids.[6–9] However, there is a need for further improvement of COPD therapy.

Phosphodiesterase-4 (PDE4) inhibition provides a novel approach to the treatment of COPD. Drugs that inhibit PDE4 have a wide range of anti-inflammatory actions in vitro and in vivo.[10–12] Roflumilast, a new PDE4 inhibitor, reduces airway inflammation in COPD, as assessed with sputum neutrophil and eosinophil counts.[13] However, although roflumilast improved lung function, it did not significantly reduce the frequency of exacerbations in unselected patients with severe COPD.[14] The results of a post-hoc analysis of this study suggested that roflumilast reduced the rate of exacerbations in patients with severe airflow obstruction, frequent exacerbations, and those requiring oral steroids.[13]

To find out whether PDE4 inhibitors can have any effect on clinical outcomes in COPD, we tested the hypothesis that roflumilast reduces the rate of exacerbations requiring systemic corticosteroids in specific subsets of patients with COPD.

Methods

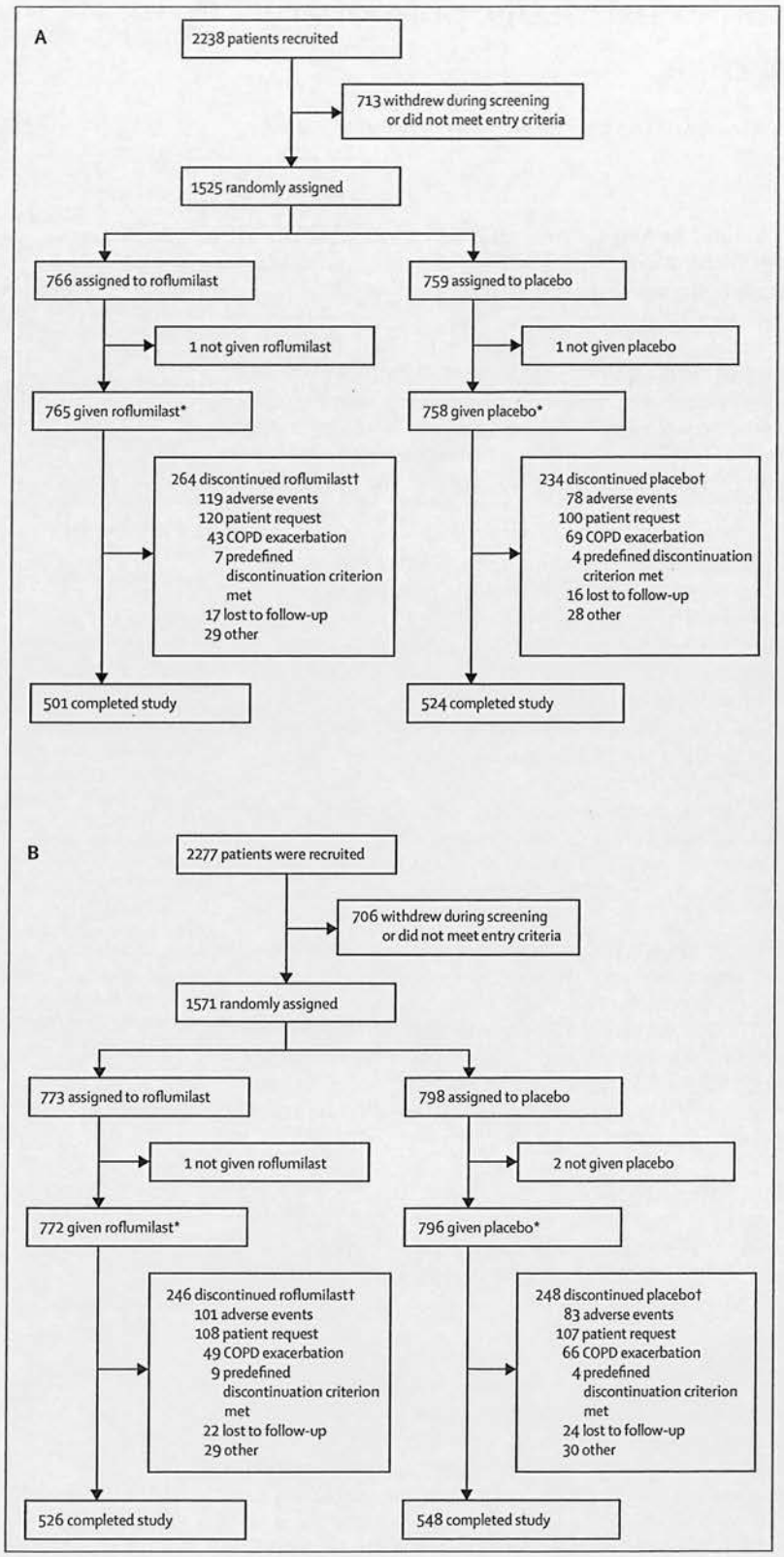
Setting

Study M2-124 was done in 246 centres in ten countries, and study M2-125 was done in 221 centres in eight countries (webappendix p 12).

See Online for webappendix

Patients

For both studies, we recruited participants from an outpatient setting if they met inclusion criteria—ie, were former smokers or current smokers with at least a 20 pack-year history, older than 40 years, and had a clinical diagnosis of COPD (confirmed with a postbronchodilator [albuterol 400 µg] forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] ratio ≤70%) and chronic



cough and sputum production. Their postbronchodilator FEV_1 was 50% or less than the predicted value. All patients had at least one recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital, or both, in the previous year. Exclusion criteria are shown in the webappendix (p 11); use of theophylline was not allowed from the start of the run-in period.

The studies were approved by local ethical review committees and done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Interventions

Each trial had an initial 4-week run-in, during which patients took a placebo tablet once a day in the morning, and recorded their use of shortacting bronchodilator drugs, and production of cough and sputum on their daily diary cards (webappendix p 23). In this initial study phase, patients, but not investigators, were unaware of the treatment they were assigned to. Patients were then randomly assigned to oral roflumilast 500 μg once a day or placebo, taken in the morning for the subsequent 52 weeks, provided that the total of their cough and sputum scores was greater than 14 in the week before randomisation, the haemoccult (guaiac) test during the baseline period was negative, at least 80% of prescribed placebo tablets were taken, and patients were clinically stable. Patients could use shortacting β_2 agonists as needed and could continue treatment with longacting β_2 agonists or shortacting anticholinergic drugs at stable doses. However, inhaled corticosteroids and longacting anticholinergic drugs were not allowed during the study. Eligible patients were stratified according to their use of longacting β_2 agonists and smoking status.

Randomisation and masking

The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients. In the double-blind treatment phase, all individuals involved in the studies were unaware of treatment assignment—tablets were identical in appearance. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling. The sponsor and clinical research associate were notified if there was a clinical reason for an individual's treatment to be unmasked by the investigator with the interactive voice recognition system.

Figure 1: **Trial profiles of M2-124 (A) and M2-125 (B)**
COPD=chronic obstructive pulmonary disease. *In the M2-124 study, one patient was randomly assigned twice and given study medication twice. The first patient number was included in the intention-to-treat and safety analyses, whereas the second patient number was only included in the safety analysis. Four patients assigned to placebo were given roflumilast instead (at least once) and were included in the roflumilast group for safety analyses. In the M2-125 study, six patients randomly assigned to placebo were given roflumilast instead (at least once) and were included in the roflumilast group for safety analyses. †Patients might have provided more than one reason for discontinuation.

	M2-124		M2-125		M2-124 and M2-125	
	Roflumilast (n=765)	Placebo (n=758)	Roflumilast (n=772)	Placebo (n=796)	Roflumilast (n=1537)	Placebo (n=1554)
Age (years)*	64 (10)	63 (9)	64 (9)	64 (9)	64 (9)	64 (9)
Men	540 (71%)	538 (71%)	610 (79%)	648 (81%)	1150 (75%)	1186 (76%)
Cigarette pack-year*†	48 (24)	46 (23)	49 (26)	47 (24)	48 (25)	47 (23)
Smoking status*						
Current smoker	365 (48%)	361 (48%)	270 (35%)	282 (35%)	635 (41%)	643 (41%)
Former smoker	400 (52%)	397 (52%)	502 (65%)	514 (65%)	902 (59%)	911 (59%)
Prebronchodilator FEV_1 (L)‡	1·07 (0·4)	1·06 (0·4)	0·95 (0·3)	0·98 (0·4)	1·01 (0·4)	1·02 (0·4)
Postbronchodilator FEV_1 (L)‡	1·16 (0·4)	1·15 (0·4)	1·05 (0·4)	1·07 (0·4)	1·10 (0·4)	1·11 (0·4)
Prebronchodilator FEV_1 (% of predicted)‡	34·7 (10·2)	34·6 (10·3)	31·4 (10·1)	32·2 (10·8)	33·0 (10·3)	33·4 (10·6)
Postbronchodilator FEV_1 (% of predicted)‡	37·6 (10·7)	37·5 (10·4)	34·6 (10·3)	35·3 (10·9)	36·1 (10·6)	36·4 (10·7)
Postbronchodilator FEV_1/FVC (%)‡	43·3 (11·6)	42·7 (11·0)	41·2 (10·7)	41·3 (10·8)	42·3 (11·2)	42·0 (10·9)
COPD severity*§¶						
Severe	486 (64%)	510 (67%)	457 (59%)	479 (60%)	943 (61%)	989 (64%)
Very severe	199 (26%)	184 (24%)	264 (34%)	256 (32%)	463 (30%)	440 (28%)
Body-mass index (kg/m^2)‡	26·4 (5·5)	26·0 (5·5)	25·2 (6·2)	25·4 (5·9)	25·8 (5·9)	25·7 (5·7)
C-reactive protein (mg/L)*	8·1 (14·0)	7·2 (12·5)	8·3 (14·6)	9·2 (17·6)	8·2 (14·3)	8·2 (15·4)
Concomitant treatment with longacting β_2 agonists‖	378 (49%)	385 (51%)	371 (48%)	408 (51%)	749 (49%)	793 (51%)
Concomitant treatment with shortacting anticholinergics‖	240 (31%)	245 (32%)	297 (38%)	324 (41%)	537 (35%)	569 (37%)
Concomitant treatment with shortacting β_2 agonists‖	761 (99%)	753 (99%)	769 (100%)	791 (99%)	1530 (100%)	1544 (99%)
Pretreatment with inhaled corticosteroids**	338 (44%)	335 (44%)	312 (40%)	322 (40%)	650 (42%)	657 (42%)
Ethnic origin						
Asian	1 (<1%)	1 (<1%)	174 (23%)	179 (22%)	175 (11%)	180 (12%)
Native American	0	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
Black	11 (1%)	15 (2%)	8 (1%)	14 (2%)	19 (1%)	29 (2%)
White	737 (96%)	732 (97%)	559 (72%)	568 (71%)	1296 (84%)	1300 (84%)
Other	16 (2%)	9 (1%)	29 (4%)	34 (4%)	45 (3%)	43 (3%)

Data are number (%) or mean (SD). FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. COPD=chronic obstructive pulmonary disease. *Measurements were taken at the beginning of the run-in period. †1 pack-year=20 cigarettes per day for 1 year. ‡Measurements were taken at baseline. §Based on the criteria of the Global initiative for chronic Obstructive Lung Disease. ¶Percentages do not add up to 100% because patients with mild or moderate COPD are not shown. ‖Based on whether the patient had used medications at least once within the start and up to the end of the treatment period inclusive. **Based on whether the patient had used inhaled corticosteroids at least once within the period starting the day after the first visit until the day before randomisation, inclusive.

Table 1: **Demographics and baseline characteristics of the intention-to-treat populations in the M2-124 and M2-125 trials**

After randomisation, patients were assessed every 4 weeks up to week 12 and every 8 weeks thereafter. At each visit, spirometric measurements were recorded before and 15–45 min after administration of bronchodilator (inhaled albuterol 400 μg). Additionally, we recorded any new exacerbations or adverse events, the patient's bodyweight, adherence to tablets, completeness of the daily diary records, use of shortacting β_2 agonists, and investigator-administered transition dyspnoea index (TDI),[15] and dispensed study medication.

Study endpoints

The primary endpoints were the change in pre-bronchodilator FEV_1 during treatment and the rate of COPD exacerbations, defined as moderate if they required oral or parenteral corticosteroids, or severe if they were associated with admission or death. Key secondary outcomes included the postbronchodilator FEV_1 (change from baseline during treatment), time to death from any cause, natural log-transformed C-reactive protein concentration (a possible marker of systemic inflammation in COPD;[16] change from baseline to study end) and TDI focal score (during treatment). A change of one unit in the TDI focal score was considered clinically significant. Additionally, data for the total number of COPD exacerbations (as defined above together with episodes treated with antibiotics alone) and a range of spirometric outcomes were gathered. As part of a planned health economic analysis (data for subsequent presentation), patients completed the Euroquol 5-dimension (EQ-5D) questionnaire, a measure of health utility, at each visit.[17]

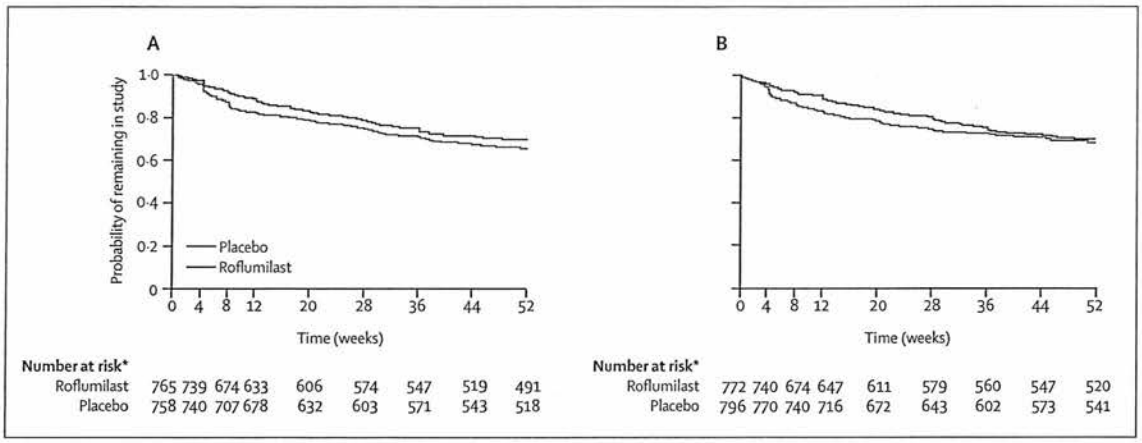


Figure 2: **Probability of treatment discontinuation in roflumilast and placebo groups in trials M2-124 (A) and M2-125 (B)**
*Number of patients still at risk at the beginning of the respective week; number at risk might be different from the number completing the study because the protocol allowed patients to finish the study up to 7 days before the end of week 52.

Bodyweight was measured with the same scales at each visit, height was measured with a stadiometer, and body-mass index (BMI) was calculated. At weeks 28 and 52 after randomisation, blood samples were taken for routine haematology and biochemistry tests, and an electrocardiogram (ECG) was done. In study M2-125, 24-h Holter monitoring was undertaken at 19 sites to identify any arrhythmias.

Statistical analysis

With the exception of the post-hoc investigation of adverse events and bodyweight, all reported efficacy analyses were prespecified in the intention-to-treat population. Data are presented as mean and SD, unless otherwise indicated. On the basis of an assumption of a mean exacerbation rate of 1·25 per patient per year in the placebo group and 1·00 in the roflumilast group, and using a Poisson regression model, with a correction for overdispersion of 2 based on previous data,[14] we estimated that 750 patients per treatment group in each trial would provide 90% power to detect a significant difference between treatments with a two-sided α level of 0·05. A negative binominal regression analysis was done to assess the robustness of the results against the distributional assumptions.

Data were analysed in the two studies separately and in a pooled analysis. We analysed changes from baseline in prebronchodilator and postbronchodilator FEV_1 using a repeated-measures analysis of covariance with all data available for patients during the 52-week treatment.[18] A Cox proportional hazard model was used to test for differences in time-to-event data. For analysis of the concentrations of C-reactive protein, an analysis of covariance model was used, with the method of the last observation carried forward for the log-transformed data for concentrations.

For the regression models (analysis of covariance, Cox, and Poisson), the covariates included treatment, age, sex, smoking status (current or former smoker), country, and treatment with longacting β_2 agonists. In the Cox analysis, country was included as a stratum. In the Poisson regression analysis, baseline post-bronchodilator FEV_1 (% of predicted value) was also included as a covariate. To address the issue of multiple comparisons, a hierarchical hypothesis-testing approach was adopted. If the primary outcomes were positive, the key secondary outcomes were tested in the order above. If a significant difference between treatments was not obtained for the primary or key secondary outcomes, all subsequent analyses were considered exploratory. No interim analyses were done in either study before unmasking. However, several statistical analyses were preplanned and done to assess the robustness of the results with respect to the effect of differential dropouts and missing data. Adverse events were analysed with descriptive statistics and 95% CIs for the differences between treatments.

The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.

Role of the funding source

All authors (academic investigators [PMAC, KFR, LMF, and FJM] and employees of the sponsor [U-MG and SK]) had full access to and interpreted the data, and were responsible for the decision to publish the report. The sponsor did not place any restrictions on the academic authors about the statements made in the final report.

Results

Patient recruitment began in February, 2006, and the studies ended in July, 2008. In the M2-124 study, 1523 patients were randomly assigned and treated (figure 1A). In M2-125, 1568 patients were randomly assigned and treated (figure 1B). Four patients in M2-124 and six in M2-125 were given roflumilast rather than placebo and are included in the treated group for

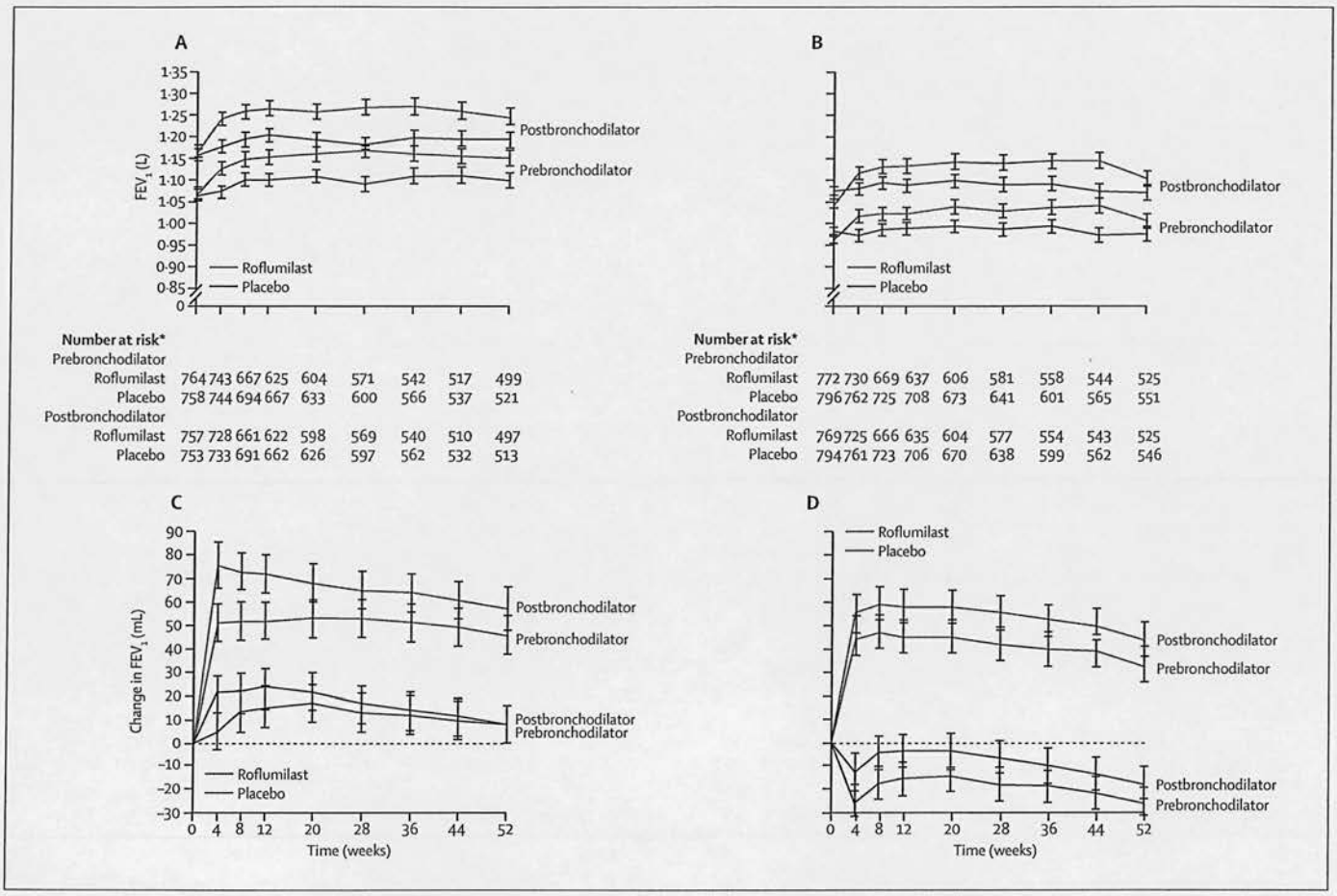


Figure 3: **Prebronchodilator and postbronchodilator forced expiratory volumes in 1 s (FEV_1) over 52 weeks in patients in roflumilast and placebo groups in trials M2-124 (A) and M2-125 (B), and changes in prebronchodilator and postbronchodilator FEV_1 over 52 weeks in patients in roflumilast and placebo groups in trials M2-124 (C) and M2-125 (D)**

The changes from baseline that could be calculated from the crude means shown in (A) and (B) are different from the changes from baseline (based on adjusted means) shown in (C) and (D): adjusted means are based on a repeated-measures analysis of covariance, including factors and covariables that might have an effect on the crude means. Error bars are SE. Number of patients at risk for the baseline value (week 0) is not equal to the number of patients in the intention-to-treat population (table 1) because some patients did not have a baseline value according to the definition from the statistical analysis plan. Two patients in the roflumilast group left the study during the last visit but were classified as non-completers because they did not undergo all investigations; hence the number of patients with FEV_1 measurements at the last visit is greater than the number of completers in figure 1B. *Number of patients with data available; number of patients reported here differs from the number at risk in figure 2 because some patients did not have their lung function measured at the end of the study, whereas others who did not complete the study had their lung function measured at week 52.

the safety analysis. Table 1 shows the demographic and baseline characteristics of the patients who took at least one dose of study medication. The only difference between the trials was the proportion of Asian patients. The mean prebronchodilator FEV_1 was between 31% and 35% of predicted value in the different study subgroups; 40–44% had used inhaled corticosteroids previously, whereas about 50% used longacting β_2 agonists during the trials (table 1).

Patient withdrawal was similar in the roflumilast and placebo groups (35% and 31%, respectively, in M2-124, and 32% and 31%, respectively, in M2-125; figure 1). However, more patients in the roflumilast group than in the placebo group withdrew in the first 12 weeks after randomisation (figure 2A and 2B). Adherence to treatment was similar in all groups: mean compliance was 93% (SD 25) in the roflumilast group and 95% (14) in the placebo group in the M2-124 study, and 93% (16) in the roflumilast group and 96% (15) in the placebo group in the M2-125 study.

The primary endpoints were achieved in both studies. Figure 3 (A to D) shows the FEV_1 data during the studies; table 2 shows the summary results. In the pooled analysis, prebronchodilator FEV_1 increased from baseline in the roflumilast group and decreased in the placebo group (table 2). The postbronchodilator FEV_1, a secondary outcome variable, increased significantly from baseline with roflumilast compared with placebo in both studies and in the pooled analysis (table 2). Prebronchodilator FVC was significantly greater with roflumilast than with placebo in both studies (table 2). Similar significant improvements were seen in postbronchodilator FVC and

	M2-124			M2-125			M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo
Lung function*									
Change in prebronchodilator FEV_1 (mL)	46 (8); n=745	8 (8); n=745	Difference 39 (18 to 60); p=0·0003	33 (7); n=730	−25 (7); n=766	Difference 58 (41 to 75); p<0·0001	40 (6); n=1475	−9 (5); n=1511	Difference 48 (35 to 62); p<0·0001
Change in postbronchodilator FEV_1 (mL)	57 (9); n=729	8 (8); n=736	Difference 49 (26 to 71); p<0·0001	44 (7); n=724	−17 (7); n=764	Difference 61 (44 to 79); p<0·0001	50 (6); n=1453	−4 (6); n=1500	Difference 55 (41 to 69); p<0·0001
Change in prebronchodilator FVC (mL)	68 (15); n=745	−21 (15); n=745	Difference 89 (51 to 127); p<0·0001	60 (14); n=730	−48 (14); n=766	Difference 108 (75 to 141); p<0·0001	64 (10); n=1475	−34 (10); n=1511	Difference 98 (73 to 123); p<0·0001
Change in postbronchodilator FVC (mL)	76 (15); n=729	−25 (15); n=736	Difference 101 (63 to 139); p<0·0001	58 (13); n=724	−45 (13); n=764	Difference 103 (72 to 134); p<0·0001	67 (10); n=1453	−35 (10); n=1500	Difference 101 (77 to 126); p<0·0001
Change in prebronchodilator FEV_1/FVC (%)	0·314 (0·223); n=745	0·001 (0·219); n=745	Difference 0·312 (−0·262 to 0·886); p=0·2858	0·200 (0·190); n=730	−0·309 (0·186); n=766	Difference 0·510 (0·061 to 0·958); p=0·0261	0·247 (0·147); n=1475	−0·146 (0·1439); n=1511	Difference 0·393 (0·028 to 0·758); p=0·0350
Change in postbronchodilator FEV_1/FVC (%)	0·488 (0·211); n=729	0·286 (0·208); n=736	Difference 0·202 (−0·343 to 0·747); p=0·4674	0·552 (0·186); n=724	−0·115 (0·182); n=764	Difference 0·668 (0·226 to 1·109); p=0·0031	0·517 (0·141); n=1453	0·090 (0·138); n=1500	Difference 0·426 (0·077 to 0·776); p=0·0169
Change in prebronchodilator FEF25–75 (mL/s)	19 (5); n=745	2 (5); n=745	Difference 17 (3 to 30); p=0·0152	15 (5); n=730	−10 (5); n=765	Difference 25 (13 to 36); p<0·0001	16 (4); n=1475	−4 (4); n=1510	Difference 20 (12 to 29); p<0·0001
Change in postbronchodilator FEF25–75 (mL/s)	22 (6); n=729	12 (6); n=736	Difference 11 (−5 to −27); p=0·1809	21 (5); n=724	−8 (5); n=763	Difference 29 (18 to 40); p<0·0001	21 (4); n=1453	2 (4); n=1499	Difference 19 (10 to 29); p<0·0001
Change in prebronchodilator PEF (L/min)	6·65 (1·45); n=745	3·58 (1·43); n=745	Difference 3·07 (−0·66 to 6·81); p=0·1063	0·75 (1·45); n=730	−3·09 (1·41); n=766	Difference 3·85 (0·46 to 7·23); p=0·0261	3·69 (1·02); n=1475	0·17 (0·99); n=1511	Difference 3·53 (1·01 to 6·04); p=0·0060
Change in postbronchodilator PEF (L/min)	8·08 (1·50); n=729	3·87 (1·48); n=736	Difference 4·21 (0·34 to 8·07); p=0·0328	1·93 (1·49); n=724	−3·14 (1·45); n=764	Difference 5·07 (1·60 to 8·53); p=0·0042	4·93 (1·05); n=1453	0·22 (1·02); n=1500	Difference 4·72 (2·13 to 7·30); p=0·0004
Exacerbations†‡									
Moderate or severe (mean rate, per patient per year [95% CI])	1·08 (0·96–1·21); n=344	1·27 (1·14–1·40); n=389	RR 0·85 (0·74 to 0·98); p=0·0278	1·21 (1·07–1·36); n=373	1·49 (1·33–1·66); n=432	RR 0·82 (0·71 to 0·94); p=0·0035	1·14 (1·05–1·24); n=717	1·37 (1·28–1·48); n=821	RR 0·83 (0·75 to 0·92); p=0·0003
Severe (mean rate, per patient per year [95% CI])	0·11 (0·07–0·15); n=69	0·12 (0·09–0·16); n=81	RR 0·89 (0·61 to 1·29); p=0·5273	0·14 (0·10–0·20); n=88	0·18 (0·13–0·25); n=117	RR 0·77 (0·53 to 1·11); p=0·1656	0·12 (0·10–0·16); n=157	0·15 (0·12–0·19); n=198	RR 0·82 (0·63 to 1·06); p=0·1334
Moderate (mean rate, per patient per year [95% CI])	0·94 (0·83–1·06); n=299	1·11 (1·00–1·25); n=343	RR 0·84 (0·72 to 0·99); p=0·0325	1·04 (0·92–1·18); n=325	1·27 (1·13–1·42); n=380	RR 0·82 (0·71 to 0·95); p=0·0075	0·99 (0·91–1·08); n=624	1·19 (1·10–1·29); n=723	RR 0·83 (0·75 to 0·92); p=0·0007
Treated with systemic corticosteroids, antibiotics, or both (mean rate, per patient per year [95% CI])	1·10 (0·98–1·23); n=336	1·30 (1·17–1·43); n=382	RR 0·85 (0·74 to 0·98); p=0·0240	1·17 (1·04–1·31); n=364	1·41 (1·27–1·57); n=416	RR 0·83 (0·72 to 0·95); p=0·0055	1·13 (1·04–1·23); n=700	1·35 (1·26–1·46); n=798	RR 0·84 (0·76 to 0·92); p=0·0003
Median time to first exacerbation (moderate or severe; days [IQR])	85·0 (29·5–185·5)	71·0 (29·0–152·0)	HR 0·88 (0·76 to 1·02); p=0·0859	73·0 (26·0–195·0)	69·5 (27·0–169·5)	HR 0·89 (0·78 to 1·03); p=0·1132	80·0 (28·0–190·0)	71·0 (28·0–160·0)	HR 0·89 (0·80 to 0·98); p=0·0185
Median time to second exacerbation (moderate or severe; days [IQR])	172·0 (102·0–253·0)	159·0 (97·0–229·0)	HR 0·79 (0·64 to 0·98); p=0·0290	188·0 (84·0–281·0)	144·0 (81·0–239·0)	HR 0·79 (0·65 to 0·97); p=0·0214	177·0 (92·0–262·0)	148·0 (85·0–236·0)	HR 0·79 (0·69 to 0·91); p=0·0014

(Continues on next page)

prebronchodilator midexpiratory flow. These changes in lung function were similar with and without treatment with longacting β_2 agonist (mean prebronchodilator FEV_1 increase with longacting β_2 agonist, 46 mL [p<0·0001] and without longacting β_2 agonist, 50 mL [p<0·0001]).

In the pooled analysis, the estimated rate of exacerbations per patient per year that were moderate or severe was 17% lower in the roflumilast group than in the placebo group (table 2). These findings were supported by the negative binomial regression analysis (data not shown). The difference in rates between treatments was independent of concomitant longacting β_2 agonist use (p=0·5382, treatment by concomitant treatment with longacting β_2 agonist interaction). The total number of exacerbations (excluding severe events) requiring treatment with systemic corticosteroids or antibiotics, or both, was also lower in the roflumilast group than in the placebo group (reduction 16%) in the pooled analysis (table 2). The times to the first and second episodes of exacerbations that were moderate or severe were significantly prolonged (table 2). When the analysis was restricted to patients who completed the

	M2-124			M2-125			M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo
(Continued from previous page)									
Further prespecified secondary analyses									
TDI focal score*	0·7 (0·1); n=741	0·4 (0·1); n=745	Difference 0·2 (0·0 to 0·4); p=0·0356	0·7 (0·1); n=729	0·4 (0·1); n=769	Difference 0·3 (0·1 to 0·5); p=0·0059	0·7 (0·1); n=1470	0·4 (0·1); n=1514	Difference 0·3 (0·1 to 0·4); p=0·0009
Change in C-reactive protein from baseline to last postrandomisation visit (mg/L)*	1·0; n=691	1·1; n=694	Difference 1·0 (0·8 to 1·1); p=0·4089	1·1; n=680	1·0; n=696	Difference 1·1 (0·9 to 1·2); p=0·3627	1·1; n=1371	1·1; n=1390	Difference 1·0 (0·9 to 1·1); p=0·8670
Time to mortality (days; mean, SD)	213·8 (118·9); n=765	207·5 (108·5); n=758	HR 1·0 (0·5 to 2·0); p=0·9212	201·0 (116·9); n=772	214·6 (137·3); n=796	HR 1·2 (0·7 to 2·1); p=0·5028	206·1 (116·4); n=1537	211·7 (125·1); n=1554	HR 1·1 (0·7 to 1·8); p=0·5452
Health utility assessment									
EQ-5D total score*	0·0049 (0·0058); n=743	0·0097 (0·0057); n=740	Difference −0·0047 (−0·0196 to 0·0101); p=0·5331	0·0100 (0·0065); n=727	−0·0006 (0·0063); n=764	Difference 0·0106 (−0·0046 to 0·0257); p=0·1715	0·0072 (0·0043); n=1470	0·0049 (0·0042); n=1504	Difference 0·0023 (−0·0083 to 0·0129); p=0·6712

Data are mean (SE), mean difference (95% CI), or point estimate (95% CI), unless otherwise indicated. n=number of patients with data available (or, for exacerbations, number of patients with at least one exacerbation). FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. FEF=forced expiratory flow. PEF=peak expiratory flow. RR=rate ratio. HR=hazard ratio. TDI=transition dyspnoea index. EQ-5D=Euroqol 5-dimension. *Least squares means (SE). †Estimated exacerbation rates were based on a Poisson regression model and HRs were based on a Cox proportional hazards model. ‡Since patients might have had more than one type of exacerbation, the total of moderate and severe exacerbations is different from the total of exacerbations that were moderate or severe.

Table 2: **Lung function variables, exacerbations, and other clinical outcomes**

trials, similar differences in exacerbation rates were seen between the groups, although these were not significant (webappendix p 13).

The preplanned sensitivity analyses confirmed the robustness of results for the primary endpoints with respect to the effect of dropouts and missing data (data not shown).

A total of 84 patients died during the studies. The mortality rates per year did not differ in the roflumilast and placebo groups in the M2–124 study (17 [2%] *vs* 17 [2%]), and in the roflumilast and placebo groups in the M2–125 study (25 [3%] *vs* 25 [3%]; hazard ratio for time to death from any cause was >1 in both studies; table 2). Baseline concentrations of C-reactive protein varied widely and did not change significantly during the study or with treatment. A small improvement was noted in TDI focal score from baseline with roflumilast compared with placebo but there were no differences in total EQ-5D scores (table 2).

Adverse events in the pooled study population were reported by 1040 (67%) patients in the roflumilast group and 963 (62%) in the placebo group; serious adverse events were reported by 301 (19%) and 336 (22%) patients, respectively. Discontinuations associated with adverse events were more common in the pooled roflumilast groups than in the pooled placebo groups (219 [14%] *vs* 177 [11%]). With the exception of COPD, the most frequent adverse events leading to discontinuation were diarrhoea, nausea, and headache in the pooled analysis (data not shown). The probability of withdrawal due to adverse events in the first 12 weeks was higher in roflumilast-treated patients (8% in both studies) than in placebo-treated patients (3% in both studies). The subsequent probability of withdrawal because of adverse events was similar between treatments (9% of roflumilast-treated patients in both studies, and 9% of placebo-treated patients in both studies).

Vomiting was reported by 17 (1%) patients in the roflumilast groups and 11 (<1%) in the placebo groups. More patients in the roflumilast than in the placebo groups had weight loss (table 3). The mean weight change was a reduction of 2·09 kg (SD 3·98) with roflumilast after 1 year and an increase of 0·08 kg (3·48) with placebo. The change in weight in the roflumilast group happened in the first 6 months of treatment and was attenuated thereafter. Patients in the roflumilast group reporting diarrhoea, nausea, vomiting, or headache had greater weight loss than did those not reporting these symptoms (2·60 kg [3·72] *vs* 2·02 kg [4·01]). The largest absolute weight loss with roflumilast occurred in obese patients (BMI>30; webappendix p 14). No differences were noted in the proportion of reported cardiovascular adverse events in the roflumilast and placebo groups (108 [7%] and 120 [8%], respectively). Atrial fibrillation was an infrequent complication reported by 17 (1%) patients in the roflumilast groups and 7 (<1%) of those in the placebo groups. There was no difference between roflumilast and placebo groups in the occurrence of rhythm disturbances in 33 and 22 Holter-monitored recordings, respectively (webappendix p 16). The incidence of pneumonia or other pulmonary infections did not increase during treatment with roflumilast (data not shown).

	M2-124			M2-125*		
	Roflumilast (n=769)†	Placebo (n=755)†	Roflumilast vs placebo (difference, 95% CI)	Roflumilast (n=778)‡	Placebo (n=790)‡	Roflumilast vs placebo (difference, 95% CI)
COPD	70 (9%)	82 (11%)	−1·76% (−4·90 to 1·38)	87 (11%)	122 (15%)	−4·26% (−7·74 to −0·78)
Diarrhoea	63 (8%)	26 (3%)	4·75% (2·28 to 7·21)	67 (9%)	23 (3%)	5·70% (3·28 to 8·12)
Weight loss	92 (12%)	24 (3%)	8·78% (6·04 to 11·53)	65 (8%)	20 (3%)	5·82% (3·46 to 8·18)
Nasopharyngitis	57 (7%)	50 (7%)	0·79% (−1·91 to 3·49)	35 (5%)	47 (6%)	−1·45% (−3·78 to 0·88)
Upper respiratory tract infection	16 (2%)	21 (3%)	−0·70% (−2·38 to 0·98)	33 (4%)	38 (5%)	−0·57% (−2·75 to 1·62)
Headache	26 (3%)	17 (2%)	1·13% (−0·66 to 2·92)	25 (3%)	8 (1%)	2·20% (0·65 to 3·75)
Pneumonia	17 (2%)	15 (2%)	0·22% (−1·35 to 1·79)	25 (3%)	16 (2%)	1·19% (−0·52 to 2·90)
Back pain	27 (4%)	22 (3%)	0·60% (−1·30 to 2·50)	23 (3%)	13 (2%)	1·31% (−0·30 to 2·92)
Acute bronchitis	35 (5%)	40 (5%)	−0·75% (−3·05 to 1·56)	21 (3%)	24 (3%)	−0·34% (−2·12 to 1·44)
Nausea	41 (5%)	15 (2%)	3·34% (1·34 to 5·35)	21 (3%)	15 (2%)	0·80% (−0·81 to 2·41)
Hypertension	20 (3%)	28 (4%)	−1·11% (−2·99 to 0·78)	18 (2%)	20 (3%)	−0·22% (−1·87 to 1·43)
Insomnia	19 (2%)	8 (1%)	1·41% (−0·04 to 2·86)	18 (2%)	12 (2%)	0·79% (−0·69 to 2·28)
Decreased appetite	21 (3%)	2 (<1%)	2·47% (1·13 to 3·81)	15 (2%)	5 (<1%)	1·30% (0·05 to 2·54)
Influenza	27 (4%)	18 (2%)	1·13% (−0·70 to 2·95)	12 (2%)	20 (3%)	−0·99% (−2·51 to 0·53)

Data are number (%), unless otherwise indicated. Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event. COPD=chronic obstructive pulmonary disease. *Incidence of adverse events in roflumilast-treated patients in study M2-125 is in descending order. †One patient was randomised twice, and included twice in the safety analysis but only once in the efficacy analysis; four patients assigned to placebo were given roflumilast instead and were included in the roflumilast group for the safety analysis; 765 patients in the roflumilast group and 758 in the placebo group were included in the efficacy analysis. ‡Six patients assigned to placebo were given roflumilast instead and were included in the roflumilast group for safety analysis; 772 patients in the roflumilast group and 796 in the placebo group were included in the efficacy analysis.

Table 3: **Adverse events occurring in at least 2·5% of patients in one of the treatment groups**

Discussion

Roflumilast reduced exacerbation frequency and induced consistent and significant improvements in FEV_1, both before and after bronchodilator use. Similar changes occurred in FVC and midexpiratory flow, suggesting a general improvement in operating lung volume. These changes were independent of the patient's smoking status or use of concomitant medication, such as inhaled longacting β_2 agonists, and were similar to those reported in other patient populations with COPD.[14,19]

PDE4 inhibition provides a novel approach to the treatment of patients with COPD. However, results from previous studies have shown inconsistent effects of PDE4 inhibitors on clinically relevant outcomes such as acute exacerbation frequency, although results from a post-hoc analysis suggested that roflumilast might be effective in selected patients with COPD.[13] The results from the M2-124 and M2-125 studies show that carefully defined patient groups that are particularly at risk of exacerbations benefit from treatment with roflumilast.

The effects of roflumilast in our proposed subgroups, which should be easily identified clinically, were tested in these two adequately powered studies with an identical design, undertaken in two geographically different populations. Participants in both studies were preselected for specific characteristics identified from earlier trials.[7,19] They had substantial airflow limitation (stages III and IV according to the criteria of the Global initiative for chronic Obstructive Lung Disease), documented cough and sputum production as a marker for persistent airway inflammation,[20] and a history of exacerbations treated in the year before entry into the study.

Many clinical trials identify patient subgroups that seem to respond to treatment in a secondary or post-hoc analysis, which is not confirmed in studies that are better powered.[21] In an earlier study, roflumilast did not reduce overall exacerbation rate but decreased the number of exacerbations requiring oral corticosteroids.[14] Data from our two studies confirmed this finding. Treatment with inhaled corticosteroids has been shown to prevent exacerbations, including those that are subsequently managed with oral corticosteroids.[7,22] The same holds true for treatment with roflumilast. A direct comparison of the effect of inhaled steroids or roflumilast on reduction of exacerbations cannot be directly assessed with the present data, but is worth investigation in the future. The rate of exacerbations in our placebo-treated patients was higher than in previous studies, with few episodes being treated with antibiotics alone, possibly because of our study design and patient recruitment. As in other 1-year trials in patients with COPD, roflumilast did not have much effect on episodes requiring treatment in hospital,[23–25] which were infrequent. In our studies, the number of patients needed to treat with roflumilast to prevent one exacerbation per year that was moderate or severe was 5·29 in the M2-124 study and 3·64 in the M2-125 study, irrespective of concurrent treatment with an inhaled longacting β_2 agonist.

Several secondary outcomes were assessed. Mortality rate during treatment did not differ between treatments

and was similar to other events during treatment in the first year of a large COPD survival trial.[7] The concentration of C-reactive protein was unaffected by treatment. However, the use of this marker in cardiorespiratory disease has been questioned.[26] Small but significant improvements in breathlessness assessed by the investigator-administered TDI occurred in both studies, but did not reach the agreed minimum clinically important difference. Whether this result indicates that the benefit of treatment with roflumilast is predominantly on prevention of exacerbations rather than improvement of exercise performance, or is a result of the selection criteria used will require further study.

Since we allowed patients to continue using inhaled longacting β_2 agonists throughout the study, and inhaled corticosteroids were withdrawn at entry, no conclusions can be drawn about synergy or interaction between roflumilast and other drugs; further studies will be needed to test specifically the effectiveness of inhaled corticosteroids alone or in combination with roflumilast. Whether the effects of roflumilast are additive to longacting inhaled bronchodilators is addressed by Fabbri and colleagues.[27] For practical reasons, the effect of roflumilast on breathlessness was tested rather than assessment of the global health status. In general, health status improves when the exacerbation rate falls by the magnitude seen here,[28,29] but confirmation of this association by means of a disease-specific instrument is needed for roflumilast. Changes in health status were not seen in the previous 1-year roflumilast study and the general health measure EQ-5D did not seem to identify differences in the data.[14] The health-care utilisation definition of exacerbations used in this study cannot precisely define the duration of events and might miss mild episodes.[30–32] In other studies with daily diary cards, substantially more events have been identified than in our studies, including many events that were not treated with corticosteroids or antibiotics. The results of a previous study have suggested that mild events associated with increased symptoms and use of shortacting β_2 agonists could be prevented with roflumilast;[19] the reduction in use of shortacting β_2 agonists that was noted in our studies supports this finding. Since roflumilast is an anti-inflammatory drug, we focused on its ability to change corticosteroid-treated exacerbations. There were fewer antibiotic-treated episodes than expected, possibly indicating the way investigators interpreted the study protocol. Interpretation of the data has been complicated by the pattern of patient withdrawal in these trials, which differed between treatment groups in the early and late phases. In general, this pattern would tend to result in a minimum biological effect of the active therapy by reducing the statistical power of the study comparisons. In accordance with good clinical trial practice, we focused on recruiting patients likely to adhere to treatment and, thus, caution is needed when generalising these findings to the general clinical population.

No significant neurological or cardiac toxicity was noted with roflumilast. A range of predicted adverse events occurred with roflumilast that were centrally mediated (insomnia, nausea, headache, but not vomiting) or gastrointestinal (predominantly diarrhoea). These were most evident in the first 4–12 weeks of treatment when they contributed to the early difference in withdrawal in both studies. Thereafter, no difference was noted between treatment groups in the occurrence of these adverse events and the withdrawals associated with them. Patients reported weight loss more frequently in the roflumilast groups than in the placebo groups, a finding confirmed by objective measurements. The mean weight loss of 2·1 kg (SD 4·0) over the course of the study was greatest in the first 6 months of roflumilast treatment. Patients reporting gastrointestinal or neurological symptoms lost more weight, but weight loss was still seen in patients without these side-effects. The change in bodyweight was similar irrespective of initial BMI and might not be an unwelcome treatment effect in obese patients who showed the largest absolute weight loss. We did not notice the occurrence of more pneumonias among patients in the roflumilast groups than among those in the placebo groups, whereas pneumonia was reported more frequently with inhaled corticosteroids in studies with similar patient-years of treatment exposure to our studies.[33] This increased frequency suggests that pneumonia might relate to local effects of inhaled corticosteroids rather than representing a general outcome of treatment with anti-inflammatory drugs in patients with COPD.

Our results from these clinical trials with identical design that were done in two different populations have shown that roflumilast, a PDE4 inhibitor, improves lung function and reduces the frequency of exacerbations in patients with bronchitic symptoms and severe airflow limitation. It should be noted that this treatment is not suitable for all patients because of the presence of class-related adverse effects that usually arise soon after initiation of treatment. Nonetheless, these results suggest that different subsets of patients exist within the broad range of COPD, and that specific therapies might improve disease management. This possibility should be explored further in prospective studies.

Contributors

All authors were members of the steering committee that developed the design and concept of the studies, approved the statistical plans, interpreted the data, and wrote the report. PMAC wrote the first draft of the report. U-MG and SK coordinated data gathering and SK did the statistical analysis. All authors vouch for the veracity and completeness of the data and the data analysis.

Conflicts of interest

PMAC has served on advisory boards for AstraZeneca, GlaxoSmithKline, Nycomed, and Novartis; received research funding from GlaxoSmithKline, Nycomed, and Boehringer Ingelheim; and spoken at meetings supported by AstraZeneca, GlaxoSmithKline, and Nycomed. KFR has served as a consultant, participated in advisory board meetings, and received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Pfizer, Novartis, Nycomed, Merck Sharp and Dohme, and GlaxoSmithKline; and received research funding from AltanaPharma, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, and GlaxoSmithKline. LMF has served as a consultant to AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck

Sharp and Dohme, Novartis, Nycomed, Roche, Pfizer, and Sigma-Tau; received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Nycomed, Roche, and Pfizer; and received grant support from AstraZeneca, Boehringer Ingelheim, Menarini, Schering-Plough, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Nycomed, Union Chimique Belge, Pfizer, Sigma-Tau, Italian Ministry of Health, and Italian Ministry for University and Research. FJM has been a member of advisory boards for GlaxoSmithKline, Schering-Plough, Novartis, Nycomed, Genzyme, Forest/Almirall, Talecris, and Roche; on the speaker's bureau for Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca; a member of steering committees for studies supported by Gilead, Actelion, Johnson & Johnson, United BioSource, and the National Institutes of Health; and an investigator in trials supported by Boehringer Ingelheim and Actelion. U-MG and SK are employees of Nycomed.

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The Effect of Helium and Oxygen on Exercise Performance in Chronic Obstructive Pulmonary Disease

CC

A Randomized Crossover Trial

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Rationale: **Breathing supplemental oxygen reduces breathlessness during exercise in patients with chronic obstructive pulmonary disease (COPD). Replacing nitrogen with helium reduces expiratory flow resistance and may improve lung emptying. Combining these treatments should be independently effective.**

Objectives: **Study the effect of changing oxygen or helium concentration in inspired gas during exercise in patients with stable COPD.**

Methods: **In 82 patients (mean age, 69.7 yr; mean FEV_1, 42.6% predicted), we measured endurance shuttle walking distance, resting and exercise oxygen saturation, and end-exercise dyspnea (Borg scale) while patients breathed Heliox28 (72% He/28% O_2), Heliox21 (79% He/21% O_2), Oxygen28 (72% N_2/28% O_2), or medical air (79% N_2/21% O_2). Gases were administered using a randomized, blinded, crossover design via a face mask and an inspiratory demand valve.**

Results: **Breathing Heliox28 increased walking distance (mean ± SD, 147 ± 150 m) and reduced Borg score (−1.28 ± 1.30) more than any other gas mixture. Heliox21 significantly increased walking distance (99 ± 101 m) and reduced dyspnea (Borg score, −0.76 ± 0.77) compared with medical air. These changes were similar to those breathing Oxygen28. The effects of helium and oxygen in Heliox28 were independent. The increase in walking distance while breathing Heliox28 was inversely related to baseline FEV_1 breathing air.**

Conclusion: **Reducing inspired gas density can improve exercise performance in COPD as much as increasing inspired oxygen. These effects can be combined as Heliox28 and are most evident in patients with more severe airflow obstruction.**

Keywords: chronic obstructive pulmonary disease; exercise capacity; helium; oxygen

Chronic obstructive pulmonary disease (COPD) is associated with impaired exercise capacity, which contributes significantly to a reduced quality of life in these patients (1). Several physiologic mechanisms limit exercise performance in COPD, but abnormal lung mechanics predominate. Unlike in healthy subjects, end-expiratory lung volume increases during exercise in patients with COPD (2). This relates to the intensity of self-reported breathlessness during exercise and is thought to result from expiratory flow limitation during tidal breathing (3).

In general, treatments improve lung emptying or decrease ventilatory requirement during exercise. Bronchodilator drugs reduce dynamic hyperinflation (4) and surgical lung volume reduction decreases static lung volumes (5). Both increase exercise capacity. Breathing supplementary oxygen during exercise significantly increases self-paced walking distance (6) and endurance time during cycle ergometer endurance exercise by reducing ventilatory demand (7–9). Similar changes occur during pulmonary rehabilitation where oxygen breathing can increase the ability to undergo training (10).

An alternative therapeutic approach would be to change the physical characteristics of the inspired gas by replacing nitrogen with the lower density gas helium. This should reduce airway resistance by decreasing turbulent flow (11) and improve respiratory gas exchange (12). This approach has been used with some benefit in the intensive care unit (13, 14), but the use of helium/oxygen gas mixtures (heliox) to increase exercise capacity has produced conflicting results in the small numbers of patients with COPD of varying severity studied (14–18).

We hypothesized that replacing nitrogen with helium would increase exercise capacity and reduce exercise-induced breathlessness in patients with stable COPD by a mechanism different to that operating when breathing supplementary oxygen. Hence, the effects of combining the two treatments would be independent of each other. Because expiratory flow limitation and the resulting turbulent air flow at high levels of ventilation will be most marked in those with severe COPD, we also hypothesized that the effects of changing the gas density would be greatest in the most severely obstructed patients. To test these hypotheses, we conducted a randomized, crossover, factorial trial to allow us to identify the independent contribution of each gas to dyspnea and exercise capacity improvement and have sufficient power to carry out subgroup analyses based on disease severity. Data from this study have been previously published in abstract form (19, 20).

METHODS

Patients

We studied patients with a diagnosis of COPD (21) confirmed by an FEV_1/FVC ratio less than 0.7, an FEV_1 less than 80% predicted, and limited bronchodilator reversibility. All patients complained of exertional dyspnea, defined by a Borg score (22) after exercise of 3 or more, and had no history of recent exacerbation. All patients were ex-smokers who continued their usual medication throughout the study. The protocol was approved by the local research ethics committees, and patients gave written, informed consent.

Measurements

Spirometry was performed breathing room air using standard criteria (23). Exercise capacity was determined using the endurance shuttle walking test (ESW), performed as described previously (24). An incremental shuttle walking test was performed initially to establish the

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walking speed corresponding to 85% of the estimated peak oxygen consumption (25). This speed was used for each subsequent ESW. In all tests, the investigator carried the gas cylinder walking beside the patient and gave no encouragement. Patients were instructed not to speak while breathing the gas mixtures and for 2 min afterwards to avoid unblinding.

Dyspnea at rest and on exercise was rated using the modified Borg category scale (22) and a 100-mm visual analog scale (VAS). Sa_{O_2} and heart rate were measured continuously with a pulse oximeter (Minolta PulseOx3i; DeVilbiss, Wollaston, UK). Values before and 5 min after breathing the test gas mixture together with the lowest Sa_{O_2} and maximum heart rate during exercise were recorded. Tympanic temperature (IVAC Corporation, San Diego, CA) was measured for 5 min at rest, before and after breathing the gas, and at end exercise.

Test Gases

Patients breathed Heliox28 (72% He/28% O_2), Heliox21 (79% He/21% O_2), Oxygen28 (72% N_2/28%O_2), or medical air (79%N_2/21%O_2) through a non-rebreathing mask and demand valve system (PRU demand valve; Oxylitre Health Care, Manchester, UK) connected to a portable cylinder (BC 2 L/200 bar; BOC Ltd., Guildford, UK). The flow resistance of this circuit was independent of the gas mixture in use.

Protocol

Patients attended four times (Figure 1). Spirometry, breathing room air, and baseline dyspnea (VAS and Borg) were assessed at each visit.

At Visit 1, the patients practiced the incremental shuttle walking test breathing room air and rated their dyspnea with the Medical Research Council breathlessness scale (26). At Visit 2, the incremental shuttle walking test was repeated, breathing medical air, to identify the subsequent ESW speed. Patients also performed a practice ESW breathing medical air. At Visits 3 and 4, patients were randomly assigned to receive two of the four gas mixtures. Two ESW tests were performed 40 min apart at each visit, one with each test gas mixture.

Statistical Analysis

Data and analyses are presented postrandomized on an intention-to-treat basis. We used a general linear model for crossover trials, comparing outcomes within subject and allowing for visit and sequence of the gases within visits (SPSS, version 11; SPSS, Inc., Chicago, IL). A Duncan's test for *post hoc* comparisons was tested for statistical significance between gases. The distance walked showed an increasing variance with increasing mean, so data were log-transformed for these analyses. In addition, exercise results are presented as untransformed values and geometric means. Results are reported as mean and 95% confidence intervals (95% CI) for normally distributed data and as mean and ranges for non–normally distributed variables unless otherwise stated.

The study sample size was established from previous studies using breathlessness as an outcome (27–29), 24 patients per center being required for full randomization.

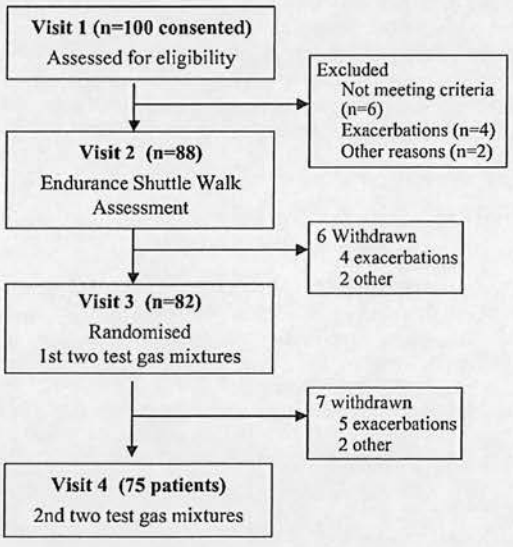

Figure 1. Study profile. A flow chart indicating the number of patients recruited to the study and their subsequent participation.

RESULTS

Patients

The progress of patients through the study is summarized in Figure 1, and the characteristics of the 82 patients randomized to receive the test gases are shown in Table 1. There was no order or visit effect with the exception of Sa_{O_2} that showed a small within-visit variation.

There was no significant change in FEV_1, baseline Borg, or VAS scores measured while breathing room air before the walking test at each visit. Walking distance, breathing medical air, was reproducible between tests ($r = 0.81$, $p < 0.001$). The mean value for ESW at Visit 2 was 258 m (95% CI, 207–310 m); at postrandomization, it was 257 m (95% CI, 201–314 m). Breathlessness at end-exercise breathing medical air was also reproducible: the mean Borg score at Visit 2 was 4.75 (95% CI, 4.06–5.44); at postrandomization, it was 4.66 (95% CI, 4.42–4.91).

No adverse effects were reported from breathing heliox gas mixtures. Tympanic temperature did not change.

Distance Walked

Patients walked significantly further while breathing Heliox28 than with either Heliox21 or Oxygen28 (Table 2). There was no significant difference between distances walked on Heliox21 and Oxygen28, but both were significantly greater than values breathing medical air. We used analysis of variance to test for any interaction between the effects of the different gas mixtures. None were found, suggesting that the effect of increasing FI_{O_2} was independent of the effect of replacing nitrogen with helium. Increasing FI_{O_2} from 21 to 28% improved endurance exercise distance by 30% (95%, CI 18–44%), replacing 79% nitrogen with 79% helium produced a 29% (95% CI, 17–42%) increase. Combining the two as Heliox28 led to a 64% (95% CI, 48–81%) improvement. Data were similar when expressed as percentage increase in endurance exercise time compared with that of medical air; Oxygen28, 32.0% (95% CI, 20.3–43.6%); Heliox21, 36.1% (95% CI, 20.4–51.8%); and Heliox28, 76.3% (95% CI, 51.3–101.3%). Patients continued exercise until they elected to stop, no data were censored by the investigators.

TABLE 1. CHARACTERISTICS OF THE 82 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE RANDOMIZED TO RECEIVE THE TEST GASES

Age, yr	69.7 (range, 46–84)
Number	82 (57 male)
FEV_1, L	1.1 (0.4)
FEV_1, % predicted	42.6 (15.5)
FVC, L	2.6 (0.8)
Sa_{O_2}, % at rest	93.9 (2.3)
BMI	25.4 (4.8)
Medical Research Council dyspnea score	3.2 (0.9)
Dyspnea score at rest	
Borg	1.8 (1.1)
Visual analog score	24.2 (19.0)

Definition of abbreviation: BMI = body mass index.
Values are mean (SD).

TABLE 2. WALKING DISTANCE, DYSPNEA, AND LIMB FATIGUE AFTER EXERCISE TOGETHER WITH OXYGEN SATURATION AT REST AND DURING EXERCISE BREATHING EACH GAS MIXTURE

	Medical Air (n = 76)	Oxygen28 (n = 78)	Heliox21 (n = 80)	Heliox28 (n = 78)	Analysis of Variance
Distance walked, m					
Arithmetic mean	257* (201–314)	330† (269–391)	354† (277–432)	389‡ (320–458)	
Geometric mean	192* (162–189)	254† (216–298)	256† (215–304)	308‡ (265–358)	$p < 0.001$
Dyspnea at end exercise					
Borg	4.7* (4.4–4.9)	4.2† (4.1–4.6)	3.9‡ (3.7–4.1)	3.4§ (3.2–3.7)	$p < 0.001$
VAS, %	68.4* (66.0–72.6)	63.3† (60.7–67.3)	62.8† (60.0–66.5)	55.5‡ (52.8–59.3)	$p < 0.001$
Limb fatigue at end exercise, Borg	2.2* (2.0–2.5)	2.1* (1.9–2.4)	2.0* (1.8–2.3)	2.3* (2.1–2.6)	
Increase in heart rate with exercise, beats/min	32.7* (27.8–37.5)	34.4* (30.1–38.6)	33.8* (30.2–37.4)	32.5* (27.5–37.5)	
Sa_{O_2}, %					
At rest					
Breathing room air	93.9* (93.53–94.27)	94.1* (93.73–94.50)	93.8* (93.5–94.2)	93.9* (93.6–94.3)	
After breathing test gas for 5 min	94.6* (94.2–94.9)	96.0† (95.7–96.4)	95.1* (94.8–95.4)	96.6‡ (96.3–97.0)	$p < 0.001$
During exercise					
Minimum reached	85.9* (85.0–86.5)	89.7† (89.0–90.5)	87.2‡ (86.5–88.0)	91.3§ (90.5–92.0)	$p < 0.001$

Definition of abbreviation: VAS = visual analog scale.

Data are expressed as mean (95% confidence interval). Duncan's test for *post hoc* comparisons was applied to determine significance between variables. Groups not sharing the same suffix differ significantly from each other. Groups sharing the same superscripted symbol do not differ significantly. Thus, for distance walked, Oxygen28 and Heliox21 did not differ from each other, but were different from medical air and Heliox28. Medical air and Heliox28 were significantly different from each other and from the other two gases.

Exercise capacity (expressed as log distance walked) breathing medical air correlated with baseline FEV_1 (Pearson correlation, $r = 0.36$), but when breathing Heliox28, this relationship was lost ($r = 0.04$). Oxygen28 and Heliox21 showed an intermediate picture ($r = 0.32$ and 0.25, respectively). The percentage increase in exercise capacity relative to the distance walked while breathing medical air is shown in Figure 2 as a box plot. When breathing Oxygen28 and Heliox21, the improvement relative to medical air was normally distributed, but there was a skewed distribution of improvement in walking distance when breathing Heliox28 (Figure 2). Some patients had a very large percentage of improvement relative to breathing medical air when breathing Heliox28. This observation was compatible with our hypothesis that patients with more severe obstruction may show the greatest benefits.

To explore this, we used analysis of covariance to model the relationship between baseline FEV_1 and percentage change in distance walked for all gases relative to that individual's walking distance when breathing medical air. The calculated regression coefficients were used to express the results of this analysis graphically (Figure 3). The size of improvement with Heliox21 and Heliox28 was negatively correlated with baseline FEV_1 ($p < 0.001$), indicating that patients with more severe airways obstruction showed the proportionately greatest increase in exercise capacity when breathing a gas mixture based on helium rather than nitrogen. Oxygen28 did not have this effect, a similar improvement in walking distance occurred irrespective of baseline spirometry.

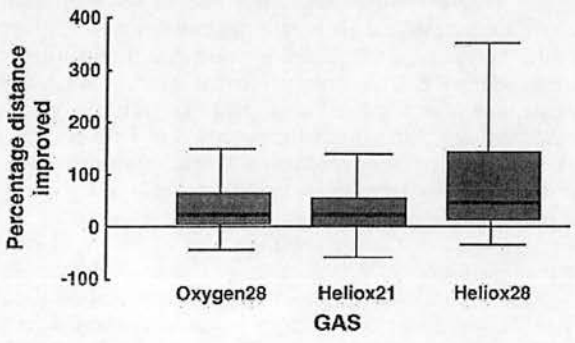

Figure 2. The percentage of improvement in walking distance breathing each gas mixture relative to that of patients breathing medical air. Data are expressed as a modified box and whisker plot with median and ± 25% boxes. The extremes of the whiskers are at 10 and 90%. The wide and asymmetric distribution around the response to Heliox28 suggests heterogeneity in the data.

Symptoms

Dyspnea. Patients' dyspnea ratings at end-exercise using the modified Borg scale were significantly different between all four gases. Breathing Heliox28 had the lowest score and medical air the highest (Table 2). The VAS scores gave similar results although the scores for Heliox21 and Oxygen28 did not differ significantly (Table 2).

Limb fatigue. Limb fatigue scores at end-exercise were unaffected by any gas mixture (Table 2). The intensity of the reported fatigue did not relate to change in distance walked nor was exercise tolerance limited by limb fatigue.

Oxygen Saturation

Patients were not significantly hypoxemic at rest (Table 1). Breathing Heliox21 for 5 min at rest did not change oxygen saturation significantly in these patients. Significant increases were found with both Oxygen28 and Heliox28, and values with Heliox28 were significantly higher than Oxygen28 (Table 2).

The minimum oxygen saturation during endurance walking differed significantly between gas mixtures (Table 2). When comparing the degree of exercise-induced desaturation, values for medical air (8.8%; 95% CI, 7.6–10.0%) and Heliox21 (7.7%; 95% CI, 6.7–8.8%) were similar, but there was significantly less desaturation breathing either Heliox28 and Oxygen28 (5.2%; 95% CI, 4.2–6.1%) and (6.2%; 95% CI, 5.1–7.3%), respectively.

Heart Rate

The increase in heart rate induced by the endurance shuttle walk breathing the four test gases was not significantly different (Table 2). These values were also similar to that found at Visit 2 breathing medical air (34.4 beats/min; 95% CI, 30.6–38.1 beats/min).

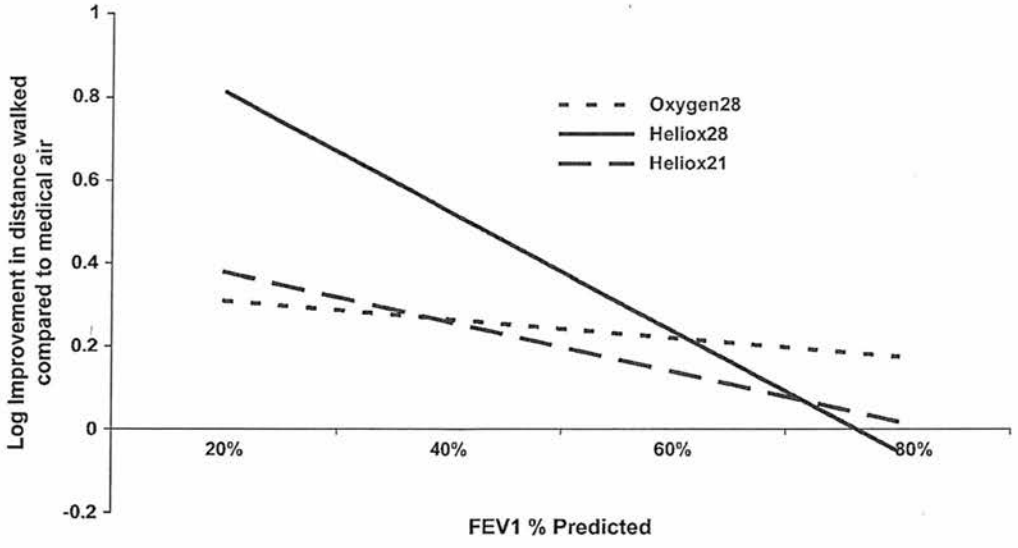

Figure 3. Relationship between baseline FEV_1 and improvement in endurance exercise capacity breathing the test gases compared with medical air. Regression slopes were calculated from an analysis of covariance and show the difference between the slope with the test gas and that obtained when breathing room air. In this model, the relationship between medical air and FEV_1 would have been zero, if plotted.

DISCUSSION

This is the first randomized controlled trial to compare the effect of increasing the inspired oxygen concentration with reducing inspired gas density on the exercise performance of patients with stable COPD. In addition, this is the first study to test whether combining these treatments produces an equivalent or an additive effect on exercise duration and dyspnea intensity.

Previous investigators have focused on identifying the underlying physiologic mechanisms that explain improved exercise performance while breathing increased oxygen concentrations (8, 9). Those observations have been confirmed in a larger number of patients using field exercise testing (30). The situation with heliox breathing in COPD has been more complicated. A number of small trials in patients with either mild (18) or very severe (17) COPD have used heliox either to explore the influence of expiratory flow limitation on exercise or as a method for unloading the inspiratory muscles (31) rather than primarily to examine its effect on exercise performance. More recently, in a single-blind randomized trial, Heliox21 was found to increase cycle endurance substantially (16). Our data in a randomized double-blind trial confirm the beneficial effect of exercising with supplementary oxygen and helium gas mixtures alone and in combination. These effects were additive in nature, but were influenced differently by the initial severity of airflow obstruction.

Earlier studies identified two rather different mechanisms by which oxygen and heliox might work, the former reducing lactate production and diminishing ventilatory drive (8, 9), whereas the latter increases maximum expiratory flow by reducing the pressure required to overcome frictional resistance and the degree of turbulence at high flow rates (16). Higher levels of minute ventilations during exercise have been reported while breathing heliox in both normal subjects and patients with COPD (18, 32). Our data confirm that patients exercising at a constant pace can walk further with a lesser degree of breathlessness when breathing 28% oxygen or a 21% oxygen/79% helium mixture, which reduces the gas density by 0.82 kg/m^3 (density: Oxygen28, 1.24 kg/m^3; Heliox21, 0.42 kg/m^3). The improvements in walking distance and dyspnea were very similar irrespective of the gas mixture used. When a modest increase of inspired oxygen was combined with a similar reduction in gas density (density Heliox28, 0.50 kg/m^3), a further improvement in walking distance and reduction in dyspnea occurred.

Distance walked was reproducible and the maximum heart rate achieved did not differ between tests, suggesting a comparable degree of cardiac stress on each occasion. However, we noted more between-subject variation in walking distance in those whose exercise performance was better preserved. We overcame this by reporting the data as log walking distance and the geometric mean distances walked derived from this analysis were very different with the different gas mixtures. Raising the inspired oxygen and Heliox21 both increased walking distance significantly. Combining the two inspired gas changes (Heliox28) increased the walking distance further and statistical analysis showed that their effects were independent. This is in keeping with their acting by independent mechanisms as suggested in previous mechanistic studies. Both gas mixtures have been shown to reduce end-expiratory lung volume during exercise, but the time course of the change in lung volume appears to be different (16). Whether changes in this measurement explain the additive effect of combining the two gas modifications should be established in future studies.

Breathing Heliox21 did not change resting oxygen saturation, which rose as expected when the inspired oxygen concentration increased. This change mitigated the degree of exercise-induced desaturation, but did not abolish it. Despite the increase in walking distance, desaturation breathing Heliox21 was significantly less than during medical air breathing, but this was still worse than with Oxygen28, which itself was worse than the desaturation breathing Heliox28. This improvement in exercise-related gas exchange may reflect better lung mechanics during exercise or improved oxygen diffusion in the presence of helium (12). In either case, the consequent reduction in ventilatory drive would decrease the degree of dyspnea experienced for any given distance covered relative to the medical air breathing test.

We observed significant heterogeneity in the response to treatment, most evident when breathing Heliox28. Because Heliox may lessen the effect of expiratory flow limitation during exercise (32) and because expiratory flow limitation occurs more frequently in patients with a reduced FEV_1 (33), we tested whether the relative improvement in exercise capacity was related to the baseline FEV_1 recorded breathing room air. In our patients, there was only a modest relationship between medical air breathing exercise distance and baseline spirometry. When breathing heliox gas mixtures, particularly Heliox28, the

correlation between walking distance and spirometry was abolished, mainly because of a greater degree of improvement in the exercise performance of patients with the worst lung function. When tested in an analysis of covariance model, we found significant differences between the responses to the different gas mixtures that were dependent on initial lung function. There was evidence of a greater proportionate benefit from heliox mixtures in patients with the worst spirometry. Breathing heliox does not appear to affect the degree of resting expiratory flow limitation (14), but its effect on lung emptying and increasing maximum exercise ventilation may be particularly important in those patients with the worse lung function who exhibit the greatest degree of ventilatory limitation on exercise. In contrast, breathing Oxygen28 produced a similar percentage improvement in performance irrespective of the initial degree of spirometric impairment, in keeping with its known effects on ventilation and lactate production.

We adopted a different approach to other studies by using a standardized endurance exercise test that reflects the conditions during exercise outside the laboratory, but still shows a good relationship with endurance exercise testing measured on the treadmill (23). Although this simpler approach restricted the data we could collect, it allowed us to study a larger number of subjects, with a wider range of baseline lung function, on repeated occasions than has been reported previously. This approach also avoided the need for recalibrating equipment between gases and hence unblinding of the investigators. Although shuttle walks are reported to have little "learning effect," we performed two practice tests before the study and used a randomized protocol to minimize any impact of such effects on the comparisons between gases. The analyses showed no sequence or order effects. We did not conduct reproducibility testing to confirm individual improvements with the heliox mixtures, but relied on the randomized blinded design to identify significant changes in group behavior. Expressing our data as walking time rather than distance might have overcome some of the intrinsic variation based on baseline performance, but this did not prove to be the case. We used two different methods of scaling breathlessness because there is no clear consensus as to which has the best measurement properties (34, 35). Grant and colleagues (36) found a clear visit effect with the VAS that was not evident with the Borg score, which we used as our principal measure of dyspnea.

Our patients were symptomatic but stable as judged by their dyspnea scores, spirometry, and exercise performance breathing medical air. We found no evidence to support the theoretic concern that the increased thermal conductivity of helium would reduce body temperature. At an individual patient level, the changes in oxygen saturation were generally too small to permit reliable identification of the gases by the investigator. We took care to avoid unblinding the patient and investigator by ensuring that the patient did not speak for at least 2 min after the end of the exercise test. In summary, we believe that there are no experimental factors that may have influenced our findings.

Our trial and other studies of supplemental oxygen have all been acute interventions performed under laboratory conditions. Future studies designed to assess the impact of heliox on daily activity will need to address technical issues concerning delivery devices for routine use. In this context, it should be noted that, despite many years of prescription of ambulatory oxygen, there is still no randomized controlled trial evidence for its benefit in daily life. Whether the substantial improvements in exercise performance and dyspnea seen with Heliox28 will translate into more effective use of ambulatory treatment remains to be determined, as will methods to identify individuals who show consistent responses to this treatment.

Although the recent American Thoracic Society/European Respiratory Society guidelines have recognized that COPD is a preventable and treatable condition (37), it is still regarded by many as one in which significant improvement is not possible. Our data show that this is not the case. The changes in endurance exercise and the reductions in breathlessness we report while breathing increased inspired oxygen or heliox gas mixtures are substantial, being at least comparable to those achieved with current bronchodilator therapy (38), pulmonary rehabilitation, or even lung volume reduction surgery (39, 40). Recent data suggest that bronchodilator therapy can enhance the effect of pulmonary rehabilitation (41), and future studies should examine whether the same is true if training is undertaken breathing Heliox28, particularly in patients with severe airflow obstruction who may have difficulty training effectively.

In selected cases, the availability of heliox therapy might have a dramatic impact on daily exercise performance and health status beyond that possible with ambulatory oxygen alone, provided Heliox28 can be administered in a way patients find acceptable. Our trial has shown that combining different treatment approaches, which modify respiratory physiology, is effective and that reducing inspired gas density by heliox breathing provides a further mechanism that can be exploited therapeutically in COPD.

Conflict of Interest Statement: E.A.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.C.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.D. has been an employee of BOC Ltd. since March 1993. M.J.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.L. was given a grant of £37,500 by BOC to assist with pulmonary rehabilitation. P.W.J. has received fees for speaking at conferences annually from 2000 to 2004 from GlaxoSmithKline (GSK), Boehringer, and Astra Zeneca at less than $5,000 per year per company; he presented as an expert witness for Boehringer in 2002 and currently receives grants from Boehringer and GSK; he has held consultancy contracts with GSK for 6 yr and sat on GSK advisory boards for 7 yr, receiving less than $5,000/yr for each of those activities separately, in each of those years; in 2004, he sat on an advisory board for Novartis and Astra Zeneca—in each case the consultancy fee was less than $5,000. P.M.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DD

Effect of oxygen on recovery from maximal exercise in patients with chronic obstructive pulmonary disease

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Background: The effects of oxygen on recovery from exercise in patients with chronic obstructive pulmonary disease (COPD) are not clearly known. A study was undertaken to determine whether oxygen given after maximal exercise reduced the degree of dynamic hyperinflation and so reduced the perception of breathlessness.

Methods: Eighteen patients with moderate to severe COPD performed maximal symptom limited exercise on a cycle ergometer. During recovery they received either air or oxygen at identical flow rates in a randomised, single blind, crossover design. Inspiratory capacity, breathing pattern data, dyspnoea intensity, and leg fatigue scores were collected at regular intervals during recovery. At a subsequent visit patients underwent a similar protocol but with a face mask in situ to eliminate the effects of instrumentation.

Results: When oxygen was given the time taken for resolution of dynamic hyperinflation was significantly shorter (mean difference between air and oxygen 6.61(1.65) minutes (95% CI 3.13 to 10.09), p=0.001). Oxygen did not, however, reduce the perception of breathlessness during recovery nor did it affect the time taken to return to baseline dyspnoea scores in either the instrumented or non-instrumented state (mean difference 2.11 (1.41) minutes (95% CI −0.88 to 5.10), p=0.15).

Conclusions: Oxygen reduces the degree of dynamic hyperinflation during recovery from exercise but does not make patients feel less breathless than breathing air. This suggests that factors other than lung mechanics may be important during recovery from exercise, or it may reflect the cooling effect of both air and oxygen.

Breathlessness is the most disabling symptom associated with chronic obstructive pulmonary disease (COPD) and its relief is an important therapeutic goal.[1] It is usually provoked by exertion and the resultant reduction in exercise capacity is itself a major determinant of impaired health status in COPD.[2 3]

Short acting bronchodilator drugs can reduce dyspnoea and increase exercise tolerance in COPD,[4 5] principally by limiting the increase in end-expiratory lung volume that occurs in this disease.[6] This is most evident in more severe disease, occurs during self-paced as well as cycle exercise,[7] and appears to be secondary to tidal expiratory flow limitation present before exercise or occurring during it.[8]

Breathing supplementary oxygen during exercise increases exercise duration and reduces the intensity of dyspnoea at any workload.[9 10] These effects occur independently of the initial arterial oxygen tension and are more evident at higher flow rates.[11] Reduction in the degree of dynamic hyperinflation secondary to a fall in minute ventilation when breathing oxygen explains most of this improvement in patients with COPD.

Much less is known about the physiological basis for "as needed" oxygen therapy in the treatment of breathlessness occurring at rest or after exercise. Patients with severe COPD are often advised to use oxygen after exercise to increase the rate of resolution of their dyspnoea.[12] However, the evidence to support this is conflicting with some studies in favour[13] but others against[14 15] there being any clinically important benefits.

In this study we hypothesised that giving oxygen at high flow rates to patients with COPD after exercise would reduce their degree of dynamic pulmonary hyperinflation and change their breathing pattern when ventilation was highest in the first 5 minutes after exercise ceased. As a result, the overall speed of resolution of their breathlessness would be increased when breathing oxygen. We anticipated that these changes would be most evident in patients with tidal flow limitation at rest where, presumably, the degree of dynamic lung volume change would be greatest. To test this we conducted a randomised, single blind, crossover trial comparing oxygen and room air given at identical flow rates and measured inspiratory capacity, breathing pattern, and dyspnoea intensity as exercise resolved. To exclude any effect of the physiological instrumentation, patients repeated the same protocol without the mouth piece and nose clip but breathing air or oxygen from a face mask, as would occur in normal clinical practice.

METHODS

Subject recruitment

Patients aged 40–79 years with stable COPD were randomly recruited from the respiratory outpatient department. COPD was defined using BTS/ERS criteria and all patients had a forced expiratory volume in 1 second (FEV_1) of <80% predicted and a ratio of FEV_1 to forced vital capacity (FVC) of <70%. Patients were excluded if they had an exacerbation of COPD, if there had been any change in their medication in the 4 weeks before the study, or if they were receiving long term domiciliary oxygen therapy. Patients unable to perform exercise testing—for example, as a result of neuromuscular problems or peripheral vascular disease—and those in whom exercise testing was contraindicated—for example, patients

Abbreviations: FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; MIP, maximal inspiratory capacity; MEP, maximal expiratory capacity; NEP, negative expiratory pressure; TFL, tidal expiratory flow limitation; TLC, total lung capacity; V_E, minute ventilation; $V_{O_2}max$, maximal oxygen consumption; $V_{CO_2}max$, maximal carbon dioxide production; V_T, tidal volume

with acute coronary syndrome—were not studied. Study approval was granted by the local research ethics committee and written informed consent was obtained.

Pulmonary function testing

Spirometric tests were performed using a rolling seal spirometer (MedGraphics 1070, Medical Graphics, St Paul, MN, USA) and met established British Thoracic Society standards. The highest value for FEV_1 and FVC from three reproducible tracings was used. Inspiratory capacity (IC) was calculated as the volume inspired from the patients' end-expiratory lung volume to total lung capacity (TLC). Satisfactory technique and reproducibility of IC manoeuvres for each subject were established initially under resting conditions and conformed to the methods described by other workers.[6] TLC was assumed to be constant throughout the exercise and recovery periods. All patients were familiarised with the exercise testing protocol before the first measurements were made. When IC was measured during exercise, the patients were warned that the measurement was about to be made a few breaths beforehand and then told: "At the end of the next normal breath, take a deep breath all the way in", together with verbal encouragement to make a maximal effort.

Expiratory flow limitation was assessed by applying negative expiratory pressure (NEP) during tidal breathing as previously described.[16] Expiratory flow limitation was deemed to be present when the application of NEP did not result in an increase in expiratory flow during most of expiration. Maximal inspiratory and expiratory mouth pressures (MIP and MEP) measured at functional residual capacity (FRC) and TLC, respectively, were assessed with a standard mouthpiece and pressure manometer (P K Morgan, Chatham, Kent, UK). Tidal breathing pattern was recorded with the patient breathing normally through a pneumotachograph (MedGraphics 1070, Medical Graphics). Computer software was used to derive timing (frequency, T_I, T_E, Ttot), tidal volume (V_T), mean inspiratory and expiratory flow (V_T/T_I, V_T/T_E), and expired minute ventilation (V_E). Oxygen saturation (Sao_2) was measured using a pulse oximeter attached to the pinna.

Exercise testing

Patients exercised on an electrically braked cycle ergometer wearing a noseclip and breathing through a mouthpiece. Ventilatory data and its derivatives were recorded breath by breath throughout the test as was oxygen consumption (Vo_2) using a fuel cell and carbon dioxide production (Vco_2) with an infrared analyser. Resting data, including the Borg symptom scores for breathlessness and leg fatigue, were recorded for 2 minutes before exercise. From 0 W the workload was increased by 10 W every 2 minutes until symptom limitation. Borg scores were recorded every 2 minutes during exercise.

Evaluation of dyspnoea and leg effort

Dyspnoea was assessed by the response to the question: "How breathless do you feel?" and leg fatigue by the question: "How tired do your legs feel?". Patients were familiarised with the modified Borg score before testing. They were asked to point to the Borg scale corresponding to their current symptom intensity at rest, during exercise, and during recovery.

Study design

Patients attended on two occasions separated by at least 1 week. At each visit resting Borg scores and oxygen saturation on air were recorded. Baseline lung function testing was performed in the same sequence for each patient at both visits and involved the measurement of flow limitation using the NEP technique, MIP and MEP, tidal breathing analysis, IC, and spirometry. Patients were advised to avoid caffeine and heavy meals for 4 hours before testing. All machines were accurately calibrated before the test sequence.

At each visit patients then performed a maximal cardiorespiratory exercise test. As soon as exercise stopped, patients randomly received either air or oxygen (Fio_2 0.4) in a single blind crossover fashion. At one visit the patient remained instrumented during recovery while at the other visit the mouthpiece and noseclips were replaced with a Venturi mask at a flow rate of 10 l/min. Patients were allowed to rest for a minimum of 45 minutes between exercise tests. When the patients remained instrumented during recovery, Borg score, tidal breathing pattern and IC were recorded every 3 minutes for 15 minutes. When patients were non-instrumented during recovery, Borg scores were recorded every minute for 15 minutes. The order of the visits was randomised in each patient, so patients were randomised to either the instrumented or non-instrumented state at the first visit with crossover at the second visit. Oxygen was administered in random order at both visits.

The study was powered on the assumption that oxygen therapy would produce a difference of 200 ml in IC by 4 minutes after exercise. This figure was selected as being equivalent to the minimum difference in IC seen with isotime comparisons when patients were receiving 60% oxygen.[17] A study of 13 patients would have a 90% power to detect such a difference. We did not power the trial on time to recovery as we had insufficient prior data to do this, although we anticipated that a significant change in IC would affect the recovery time. Likewise, data about the speed of symptomatic recovery in this patient group was lacking and we accepted that any change in symptom recovery time that achieved statistical significance would be of clinical interest in a study of this size.

Statistical analysis

Descriptive data are expressed as mean (SD) while other statistical data are expressed as mean (SE). Single paired comparisons were performed using Student's *t* tests and non-parametric data were analysed using the Wilcoxon rank sum test. Repeated measures data were analysed using summary measures over time which are expressed as mean (SE) with 95% confidence intervals (CI). When data involved more than one comparison, ANOVA was used to assess the significance of differences between the groups, a p value of <0.05 being accepted as significant for all analyses.

RESULTS

Subjects

Fifty four patients were screened of whom 38 met the study criteria and 18 agreed to participate. One patient declined to attend for visit 2, during which recovery was randomly allocated to be non-instrumented. There were no statistical differences in baseline pulmonary function between visits (table 1). No patient was hypoxaemic at rest, although six patients desaturated during the maximal cardiorespiratory exercise test—the lowest Sao_2 was 88% (range 88–96%) and the longest period of desaturation was 6 minutes. Patients who desaturated with exercise had a lower baseline FEV_1 than those who maintained their Sao_2 constant when exercising (0.73 (0.09) l *v* 1.26 (0.09) l; $p = 0.01$). Four of the six patients who desaturated also exhibited tidal flow limitation at rest.

The presence of desaturation during exercise did not influence the subsequent results of oxygen treatment.

At each of the four cardiorespiratory exercise tests the mean (SD) duration of exercise (8.02 (0.39) minutes) and

Table 1 Baseline anthropometric and resting lung function data

No of patients	18
Sex (M:F)	12:6
Age (years)	61.2 (4.4)
FEV_1 (litres)	1.08 (0.42)
FEV_1 (% predicted)	40.28 (15.93)
IC (litres)	2.17 (0.64)
IC (% predicted)	86.88 (25.27)
MIP (cm H_2O)	70.18 (16.47)
MEP (cm H_2O)	105.28 (21.98)
SaO_2 (%)	95.94 (1.66)
Resting Borg breathlessness score	0.84 (0.87)
Resting Borg leg score	1.0 (1.12)
TFL	7/18

Values given are mean (SD) of visits 1 and 2.
FEV_1, forced expiratory volume in 1 second; IC, inspiratory capacity; MIP, maximal inspiratory capacity; MEP, maximal expiratory capacity; TFL, tidal expiratory flow limitation.

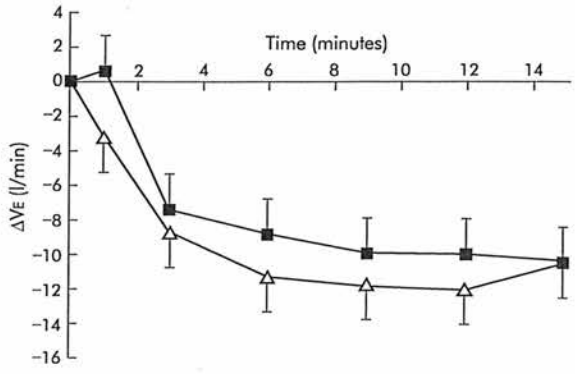

Figure 1 Change in minute ventilation (VE) over time after the end of exercise when breathing oxygen (open symbols) and breathing air (solid symbols). No significant difference in VE was seen between the gas mixtures.

maximal workload (37.5 (3.98) W) were not significantly different (table 2). In addition, there was no statistical difference between tests in the maximum Borg breathlessness and leg scores achieved (mean (SD) 5.30 (2.04) and 5.30 (1.94), respectively).

Seven patients had expiratory flow limitation during tidal breathing at rest in the seated position. FEV_1 did not differ significantly between patients with and without flow limitation (0.88 (0.13) l *v* 1.21 (0.14) l; $p = 0.09$). In addition, Borg breathlessness scores at rest did not differ significantly between patients with and without flow limitation (0.75 (0.44) *v* 1.27 (0.28); $p = 0.31$). In most patients ($n = 16$) IC was lower when measured 1 minute after the end of exercise, reflecting dynamic hyperinflation. The two patients who did not show evidence of hyperinflation at this time were not flow limited at rest; however, their baseline FEV_1 was not statistically different from that of patients who exhibited dynamic hyperinflation.

Ventilation, breathing pattern, and lung mechanics after exercise

The mean (SD) resting VE at both visits was 14.46 (5.28) l/min. During maximal exercise this increased to 23.68 (4.84) l/min. The mean (SE) difference in VE over the recovery period between air and oxygen was 0.79 (0.58) l/min (95% CI −0.71 to 2.29); $p = 0.24$ (fig 1). Mean (SE) baseline VT was 0.75 (0.05) l which increased to 0.89 (0.02) l at maximal exercise. Breathing frequency was 21.33 (1.18) breaths/min at baseline, peaking at 28.53 (0.70) breaths/min at maximum exercise. Neither VT nor breathing frequency was affected by oxygen at any time during recovery.

At baseline, mean (SD) IC at both visits was 2.22 (0.62) l. One minute into the recovery period the mean (SD) IC was 2.01 (0.56) l. Patients with resting expiratory tidal flow limitation, as assessed by the NEP technique, did not have greater dynamic hyperinflation at this point after exercise. By 4 minutes after exercise the IC in the oxygen treated patients was significantly less than in those breathing air ($p<0.01$; fig 2). The mean (SE) difference in IC during recovery between air and oxygen was −0.27 (0.13) l (95% CI −0.60 to 0.07); $p = 0.07$). The time taken for resolution of dynamic hyperinflation was significantly shorter when oxygen was administered (mean difference between treatments 6.61 (1.65) minutes (95% CI 3.13 to 10.09); $p = 0.001$). This was true for patients with and without tidal flow limitation at rest.

The mean (SD) Borg breathlessness score at rest in all four tests was 0.87 (1.02), rising to 5.30 (2.04) at maximal exercise. Breathlessness scores fell with recovery. There was no statistical difference in Borg scores at any time during recovery between oxygen and air irrespective of the presence of instrumentation, nor was the time to return to the pre-exercise level of breathless affected by the gas inhaled (fig 3). The mean (SE) difference in Borg breathlessness scores over the recovery period when instrumented was 0.009 (0.12), (95% CI −0.21 to 0.39); $p = 0.47$. When non-instrumented, the mean (SE) difference in Borg score over time was −0.14 (0.007), (95% CI −0.31 to 0.00); $p = 0.10$. In the instrumented

Table 2 Ventilatory, breathlessness, and leg fatigue data at rest and maximal exercise for each of the four cardiorespiratory exercise tests

Test	Air with mouthpiece	Oxygen with mouthpiece	Air with mask	Oxygen with mask
Resting Borg breathlessness score	0.97 (0.28)	0.75 (0.25)	1.03 (0.26)	0.74 (0.21)
Resting Borg leg score	1.06 (0.31)	1.03 (0.25)	0.94 (0.27)	0.97 (0.26)
Exercise duration (minutes)	8.16 (0.96)	7.07 (0.87)	8.18 (0.95)	8.65 (0.98)
Maximal exercise Borg breathlessness score	5.36 (0.55)	5.17 (0.51)	5.26 (0.49)	5.41 (0.51)
Maximal exercise Borg leg score	5.56 (0.47)	5.19 (0.39)	5.00 (0.50)	5.44 (0.52)
Maximal workload (W)	37.22 (5.53)	32.78 (5.47)	38.23 (5.30)	41.18 (5.55)
V_{O_2} max (l/min)	0.97 (0.09)	0.94 (0.08)	0.94 (0.08)	0.91 (0.07)
V_{CO_2}max (l/min)	0.85 (0.08)	0.82 (0.08)	0.83 (0.07)	0.82 (0.07)

Values are mean (SE).
V_{O_2}max, maximal oxygen consumption; V_{CO_2}max, maximal carbon dioxide production.
Statistical analysis between groups was performed using ANOVA. All p values >0.05.

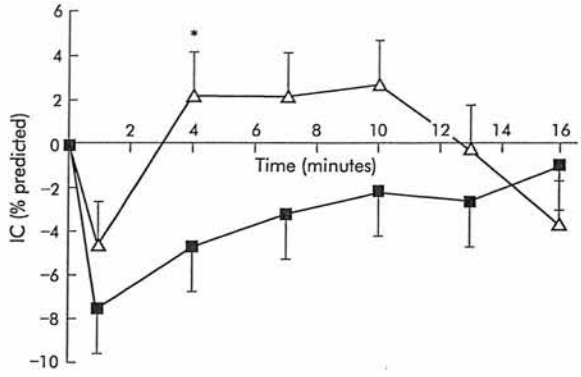

Figure 2 Change in inspiratory capacity (IC) expressed as a percentage of predicted value for age and height during recovery from exercise when breathing oxygen (open symbols) and breathing air (solid symbols). IC fell after exercise and returned to baseline values during recovery. It was significantly greater at 4 minutes when breathing oxygen than when breathing air; *$p<0.01$. The rate of recovery of IC was more rapid during oxygen breathing although overall the difference in IC at all time points was not significantly different.

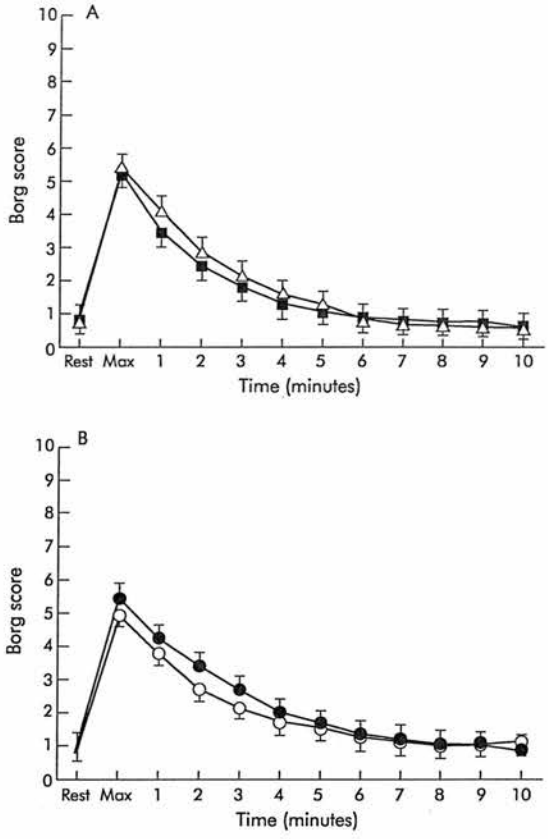

Figure 3 Borg score for breathlessness before and after exercise in (A) patients breathing oxygen (open symbols) or air (solid symbols) with nose clip and mouthpiece and (B) patients breathing from a face mask.

patients the time taken to return to the baseline dyspnoea score was not significantly different when breathing oxygen (mean (SE) difference between air and oxygen 2.11 (1.41) minutes (95% CI −0.88 to 5.10); $p = 0.15$). Similarly, when patients were non-instrumented there was no difference in the time to symptomatic recovery between gases (mean (SE) difference between air and oxygen 0.47 (0.46) minutes (95% CI −0.51 to 1.45); $p = 0.32$). However, the time take for the dyspnoea score to return to the baseline levels was greater when breathing air through the mouthpiece than when it was administered from a face mask (mean (SE) difference 3.94 (1.77) minutes (95% CI 0.20 to 7.69); $p = 0.04$).

The mean (SD) Borg score for leg effort was 1.00 (1.12) at rest and increased to 5.30 (1.94) at maximal exercise. Leg fatigue scores were not statistically different at any point during recovery when breathing oxygen. In addition, the time taken to return to baseline scores did not differ when oxygen or air was administered. The mean (SE) difference between air and oxygen in the time taken to return to baseline was 0.65 (1.07) minutes (95% CI −1.62 to 2.91); $p = 0.55$.

DISCUSSION

Although there is good evidence for the clinical benefit of oxygen administration during exercise in patients with COPD, equivalent data supporting the use of oxygen to help breathlessness resolve more rapidly when exercise stops are scanty.[18] Despite this, most cylinder oxygen in the UK is prescribed for this purpose and to control acute dyspnoea, an indication where there is some experimental evidence of effectiveness.[19 20] Since the completion of our study further data have been published showing that oxygen after exercise does not appear to influence the rate of symptomatic recovery.[15 21] Our data using a more robust trial design suggest that supplementary oxygen does reduce dynamic hyperinflation more rapidly than breathing room air after exercise stops. However, this does not translate into a significant reduction in the degree of dyspnoea at any time after exercise, nor does it influence the rate at which symptoms resolve.

In this study we used a standardised progressive exercise protocol to produce the same level of breathlessness before giving either air or oxygen, something not always done in previous studies. The duration of exercise and degree of metabolic load incurred were similar in each test. The degree of oxygen desaturation observed during or at the end of exercise did not influence the subsequent symptomatic response to oxygen breathing. We measured IC before and soon after exercise ended to allow time for the inspired gas to have an effect. As a result, our IC values were somewhat lower than those recorded at maximum exercise or immediately after stopping walking.[7 22] As our purpose was to compare the effect of oxygen and air on dynamic inflation, we did not relate these data to peak values during exercise. The need to obtain technically satisfactory measurements and to record symptom intensity determined the timing of the measurements during the recovery period. In practice, most of the change in dynamic hyperinflation and symptoms occurred 3–6 minutes after exercise ended.

Breathing oxygen (Fio_2 0.4, flow 10 l/min) did not significantly affect either ventilation or breathing pattern during the recovery period. The apparent early difference in ventilation seen in fig 1 was not accompanied by consistent changes in ventilation at other time points during recovery. The degree of dynamic hyperinflation was different by 4 minutes after exercise and this probably explains the more rapid resolution of this phenomenon during oxygen breathing. As different individuals recover at different times after exercise ends, it is not surprising that there is more "noise" in the latter measurements and it is proportionately harder to demonstrate changes in related variables such as ventilation and breathing pattern than is the case during endurance

exercise testing. Nonetheless, oxygen does reduce the degree of dynamic hyperinflation more rapidly but, in contrast to the situation during exercise, this does not appear to be the major determinant of dyspnoea.

Perception of breathlessness and leg effort

Dynamic hyperinflation occurs more frequently in patients with expiratory flow limitation at rest[23] and can be reduced by oxygen breathing at rest.[20] We did not find a clear association with tidal expiratory flow limitation and the presence of dynamic hyperinflation 1 minute after exercise in our patients. This may reflect the onset of flow limitation during exercise as noted by others.[24] In our patients the presence of resting expiratory flow limitation did not identify a subgroup more responsive to supplementary oxygen.

The failure of oxygen to affect dyspnoea intensity reflects the different conditions present after exercise compared with those during exercise. When patients with COPD exercise there is a progressive rise in the respiratory drive to breathe due to metabolic CO_2 production, increasing blood lactate concentrations, and changes in arterial blood gas tensions. In these circumstances any factor that reduces ventilatory drive—such as supplementary oxygen—will modify the breathing pattern, improve lung emptying, reduce dynamic hyperinflation, and lessen dyspnoea. After exercise the metabolic drive to breathing declines exponentially whatever gas mixture is inhaled at a speed that is influenced by many factors including the redistribution of regional blood flow, lactate metabolism, and any co-existing cardiac dysfunction. Although changes in dynamic lung volume still occur, their relative importance is less than the declining central respiratory drive and does not appear to significantly affect the intensity of dyspnoea.

Although oxygen did not influence the intensity or rate of resolution of symptoms, the presence of a mouthpiece and noseclip did. This may explain some of the differences in recovery time from exercise previously reported in the literature. We chose high gas flow rates to ensure that the optimal effect on dyspnoea was achieved[11] but, in doing so, may have provided some relief from dyspnoea with both gas mixtures, the facial and upper airway cooling effect being known to reduce dypnoea during exercise in COPD.[25]

Our data help to explain why oxygen has less effect as symptomatic treatment than might be anticipated from its known effects during exercise, and support recently reported data on this topic.[15] Administration of oxygen or compressed air may be a useful way of providing a source of cooling gas flow, but other cheaper and more convenient methods of doing this are worth exploring in future trials. The routine use of oxygen to aid recovery of symptoms after exercise does not appear to be warranted.

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Effect of oxygen on recovery from maximal exercise in patients with chronic obstructive pulmonary disease

N J Stevenson and P M A Calverley

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EDITOR'S CHOICE

Lower limb activity and its determinants in COPD

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► Additional Methods and Results data are published online only at http://thorax.bmj.com/content/vol63/issue8

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ABSTRACT

Background: Patients with chronic obstructive pulmonary disease (COPD) walk less than healthy older people and their self-reported activity predicts exacerbation risk. The relationship between lower limb activity and total daily activity is not known, nor are there any data which relate objectively assessed daily activity to laboratory assessments made before and after rehabilitation.

Methods: Lower limb activity was measured by leg actigraphy over 3 days in 45 patients with moderate to severe COPD and 18 controls of similar age. Thirty-three patients with COPD entered an 8-week rehabilitation programme in which the change in leg activity was measured and related to other outcomes.

Results: In patients with COPD the mean level of activity measured by whole body and leg activity monitors was closely related ($r = 0.92$; $p<0.001$), but leg activity was consistently reduced compared with controls of similar age ($p = 0.001$). Mean leg activity, mean intensity of leg activity and the time that patients spent mobile at home were all related to forced expiratory volume in 1 s (FEV_1) ($r = 0.57$, $p = 0.001$; $r = 0.5$, $p = 0.003$; and $r = 0.51$, $p = 0.002$, respectively), but intensity of activity and time spent mobile were not related. Subjects completing pulmonary rehabilitation showed significant improvements in mean activity ($p = 0.001$) and spent more time moving ($p = 0.014$). These changes were unrelated to improvement in muscle strength or walking distance but correlated with baseline FEV_1 ($r = 0.8$, $p<0.001$).

Conclusions: Total daily activity in patients with COPD is closely related to leg activity which is reduced compared with controls of similar age. Individuals differ in the time spent mobile during the day, but subjective and objectively assessed activity improves after rehabilitation and is predicted by FEV_1. The change in activity is unrelated to improvements in corridor walking and health status.

Symptomatic chronic obstructive pulmonary disease (COPD) is associated with impaired exercise performance which, in turn, is related to a reduction in health status[1] and mortality.[2] Conventionally, this impairment has been documented by incremental or endurance exercise testing often using field exercise tests such as the 6 min walking distance[3] or the endurance shuttle walking test.[4] However, exercise testing measures what an individual is capable of doing rather than their activity. The level of activity reported by patients with COPD relates to the risk of hospitalisation after an exacerbation[5] and mortality.[6] More recently, the availability of reliable accelerometers has made it possible objectively to monitor daily activities outside the laboratory. Patients with COPD are less active than healthy age-matched controls and spend longer sitting and lying down,[7] while activity improves after a rehabilitation programme irrespective of the exercise regime used.[8]

To date, home activity monitoring has reported total body movements over a 12 h period using a waist-mounted triaxial accelerometer which, in the case of the Dynaport system, also reports the type of activity.[9] The amount of total daily activity resulting from lower limb movement has not been determined. This is important as patients with COPD are subject to loss of skeletal muscle mass which is most evident in the legs,[10] and reduced quadriceps strength predicts both healthcare use[11] and future mortality.[12]

We hypothesised that the degree of leg activity would be an important determinant of the total daily activity of patients with COPD. In addition, leg activity would relate both to self-paced walking distance and muscle strength and would improve significantly after pulmonary rehabilitation. Moreover, we anticipated that the initial degree of activity impairment would predict the extent to which activity improved after rehabilitation, whether this was assessed objectively by activity monitoring or subjectively by activity questionnaire. To test these hypotheses, we have monitored activity simultaneously with a leg-mounted accelerometer and a Dynaport activity monitor and subsequently related leg activity to well-recognised outcome measures before and after pulmonary rehabilitation.

METHODS

Subjects

Patients with a clinical and physiological diagnosis of COPD[13] who had not used antibiotics or oral corticosteroids for at least 6 weeks and who were referred for pulmonary rehabilitation were recruited to the study. Medication was individually optimised before assessment and remained constant throughout the study. Patients using domiciliary oxygen, those with unstable cardiac disease, and those unable to exercise due to musculoskeletal, neurological or vascular disorders were excluded. All patients provided written informed consent and the protocol was approved by the local research ethics committee.

Study protocol

Patients participated in one or more of three study evaluations.

- Evaluation 1: A subset of patients with COPD underwent simultaneous leg accelerometry measurements and total body activity measurements. These subjects also completed health status and activity questionnaires.
- Evaluation 2: In a second group of patients with COPD, leg accelerometry measurements were compared with those of a control group of

healthy volunteers of similar age and sex. Quadriceps muscle strength was also recorded.

- Evaluation 3: A third group of patients with COPD completed leg accelerometry measurements before and after pulmonary rehabilitation and these leg activity data were related to standard measures of lung function, exercise performance, muscle strength and health status.

Before rehabilitation, assessments were performed on two visits approximately 7 days apart. After rehabilitation, all assessments were completed on a single visit scheduled no more than 14 days after completion of the exercise programme. Each subject performed the same tests in the same order. All tests were performed before and after rehabilitation with the exception of lung function measurement and the two practice 6 min walks.

Procedures

Pulmonary function tests

Before testing, patients omitted short-acting inhaled bronchodilators for 8 h and long-acting β agonists for 12 h. Spirometry, static lung volumes and single breath carbon monoxide transfer factor were measured with a rolling seal spirometer (P K Morgan, Kent, UK) according to American Thoracic Society guidelines.[14] Static lung volumes were measured by helium dilution. Predicted values used were those of the European Coal and Steel Community.[15]

Heath status and disability questionnaires

Patients completed the St George's Respiratory Questionnaire (SGRQ)[16] and the Hospital Anxiety and Depression (HAD) questionnaire,[17] while self-reported activity was assessed using the Nottingham Extended Activities of Daily Living (NEADL) questionnaire.[18]

Quadriceps muscle strength

Maximum quadriceps strength was measured by isometric maximum voluntary contraction of the dominant quadriceps using a custom-built set up. Further details of this are included in the online supplement. Subjects performed three maximum voluntary contractions with a rest period of 1 min between efforts. Maximum quadriceps strength was defined as the peak value obtained from the three recordings.

Six minute walking test

The tests were performed in accordance with ATS recommendations[19] with two additional practice walks at the initial assessment. Perceived breathlessness was scored immediately before exercise and at maximum exercise using the modified Borg scale.[20]

Activity measurement

Leg accelerometry measurement

Leg activity was measured using the Actiwatch Uniaxial Accelerometer (Cambridge Neurotechnology, Cambridge, UK). All recordings were made continuously over three weekdays with the exception of Evaluation 1 (comparison of whole body and lower limb activity) where only 2 days were recorded. Using a lightweight strap, the Actiwatch was positioned just above the dominant ankle and subjects only removed the device for bathing and then repositioned the Actiwatch immediately afterwards. The Actiwatch has an event marker button and subjects pressed this button on rising in the morning, going to bed at night and when the device was removed for bathing. Subjects also documented when and why the activity monitor was removed. On the rare occasion a subject forgot to press the marker button, the written record or period of overnight inactivity was used to determine the actigram. Activity monitoring was performed before and after rehabilitation with the same Actiwatch.

The Actiwatch signal is measured 32 times per second and processed to provide the amount and duration of movement. This signal is expressed as an activity count which denotes the amplitude of the signal detected by the accelerometer. A vale of approximately 25 counts represents gravitational acceleration. Further details about the technical specifications are given in the online supplement. Data were expressed as an activity count, which is the sum of all the epochs within each 30 s period. Inactivity was expressed as an activity count of zero. Data extracted for analysis were aggregated over the three daytime periods and expressed as:

- Mean activity score: average value of each 30 s epoch throughout the waking day, including all periods of zero activity.
- Mean intensity of activity: average value of each 30 s epoch when activity was occurring throughout the waking day (excludes any period of zero activity).
- Percentage of time mobile: percentage of 30 s epochs throughout the waking day where an activity score of ≥ 1 was recorded; any epoch with a mean activity score of 0 was labelled immobile, while any epoch with a score of ≥ 1 was active, although a score of 1 represents a very low level of activity.

Total body activity measurement

The Dynaport Activity Monitor (McRoberts BV, Den Haag, Netherlands) is a lightweight device containing a triaxial accelerometer. It has previously been validated for use in patients with COPD.[9] The device consists of a lightweight box enclosed in a neoprene belt worn anteriorly around the waist. The box is connected to a leg sensor which is worn around the upper third of the thigh. The signal recorded by the device precisely measures the time spent walking, cycling, standing, sitting or lying, and it also provides a measure of movement intensity during the recording period. The technical specifications of the activity monitor have been detailed previously.[21]

The Dynaport Activity Monitor provides a measure of overall activity (movement intensity) and a measure of intensity of activity (movement intensity during movement). In addition, it records the proportion of the day during which the subject was moving (time spent moving). Different activities can be classified and expressed as the proportion of the day spent walking, standing, sitting and lying down.

The Dynaport Activity Monitor was fitted and all subjects were provided with written instructions, spare batteries and an emergency contact number. The subjects were monitored for two consecutive days, a time period over which reliable results have been obtained previously.[7] Monitoring lasted from rising in the morning until whatever time in the evening they had completed their usual daily activities.

Pulmonary rehabilitation

The 8-week outpatient pulmonary rehabilitation programme consisted of two supervised and one unsupervised 1-hour exercise session per week. Patients received an individualised regime of aerobic upper and lower limb exercises which included peripheral muscle strengthening and whole body endurance exercises. Further details of the programme are included in the

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Table 1 Baseline characteristics and number of subjects in each study evaluation

	Evaluation 1 (subjects with COPD who had concurrent DP and AW measurements)	Evaluation 2 (normal subjects of similar age who had AW measurement)	Evaluation 3 (subjects with COPD who had AW measurement before and after PR)	Evaluations 2 and 3 (subjects with COPD who had AW measurement)
No of subjects	12	18	23	33
M:F	9:3	8:10	12:11	17:16
Age (years)	63 (7)	70 (6)	66 (9)	67 (8)
Current:ex:never smokers	3:9:0	5:9:4	5:18:0	7:26:0
FEV_1 (l)	1.01 (0.43)	2.5 (0.6)	0.93 (0.32)	0.96 (0.4)
FEV_1 (%)	33.4 (12.2)	105.1 (17.7)	36.4 (11.6)	38.2 (12)
FVC (l)	2.83 (0.93)	3.3 (0.8)	2.27 (0.46)	2.36 (0.9)
FEV_1/FVC	0.36 (0.07)	0.77 (0.04)	0.41 (0.13)	0.42 (0.12)
IC%	73.3 (14.5)	NK	71.6 (15.8)	77.6 (20.8)
Quadriceps MVC (N)	NK	415 (98)	315 (106)	308 (116)
SGRQ Total	63.4 (16.2)	NK	62.1 (13)	62.2 (12.5)
SGRQ Activity	77.2 (19.4)	NK	79.1 (13.1)	80.1 (13.7)
NEADL	18.9 (2.3)	NK	16.4 (2.7)	15.7 (2.8)
Actiwatch measures:				
Mean activity ($\times 10^3$ counts/h)	123 (110)	143 (61)	82 (53)	82 (49)
Mean intensity of activity ($\times 10^3$ counts/h)	190 (162)	232 (90)	156 (69)	156 (63)
% of time mobile	63.2 (14.5)	61.4 (11.2)	50 (13.9)	50.8 (15.4)

Data presented as mean (SD).
AW, measurement of leg activity using the Actiwatch accelerometer; COPD, chronic obstructive pulmonary disease; DP, measurement of whole body activity using the Dynaport activity monitor; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; MVC, maximum voluntary contraction; NEADL, Nottingham Extended Activities of Daily Living Questionnaire; NK, not known (not recorded in the particular group); PR, pulmonary rehabilitation; SGRQ, St George's Respiratory Questionnaire.

online supplement. Owing to the "rolling" nature of the programme, subjects who were unable to attend particular supervised session(s) were able to continue the programme beyond 8 weeks until they had attended 16 supervised sessions. Patients who attended 16 sessions were defined as "completers".

Statistical analysis

Group data are expressed as mean (SD) and subgroup data as mean (SE). Statistical analysis was performed using SPSS V.15.0 and Stats Direct 2.6 with significance set at $p<0.05$; p values are recorded to three decimal places. Normal distribution was assessed using the Shapiro-Wilks test and all data were normally distributed except for the Actiwatch mean activity score and Actiwatch mean activity score when active. These data were logarithmically transformed to normalise the distribution. Paired and unpaired Student *t* tests were used to detect differences in group data and Pearson's correlation coefficient was used to examine the association between individual parameters. Multiple linear regression analysis was performed with the primary explanatory variables being change in activity scores after pulmonary rehabilitation. A model was constructed to examine the following potential exploratory variables: forced expiratory volume in 1 s (FEV_1) in litres, FEV_1 percent predicted, ratio of FEV_1 to forced vital capacity (FVC), carbon monoxide transfer factor (TLCO) percent predicted, quadriceps strength, 6 min walking distance, SGRQ score and NEADL score. The final model was constructed using a backwards stepwise procedure; at each step a variable was removed which reduced the amount of variation accounted for by the least amount. Using published data, we considered an improvement in 6 min walk distance of 54 m after completion of pulmonary rehabilitation to be clinically significant.[3] From pilot data we established that a change in Actiwatch mean activity score of 30 corresponded with similar improvements in walking distance and an improvement in health status. Based on the change in these two measures, we established that 24 subjects had to complete evaluation 3 of the study to detect a difference in these outcomes with 80% power at a significance level of 5%.

Table 2 Measurements of activity obtained by the Actiwatch (leg) and Dynaport (whole body) systems during the 2 days of recording in 12 patients with chronic obstructive pulmonary disease (Evaluation 1)

	Mean (SD)
Actiwatch	
Time spent mobile (% of recording)	63.3 (14.5)
Mean activity score ($\times 10^3$ counts/h)	123 (110)
Mean intensity of activity ($\times 10^3$ counts/h)	190 (162)
Dynaport	
Time spent moving (%)	13.5 (4.4)
Movement intensity	0.2 (0.1)
Movement intensity during movement	1.48 (0.21)
Time spent walking (%)	3.6 (2.8)
Time spent standing (%)	32.1 (15.2)
Time spent sitting (%)	58.7 (17.6)
Time spent lying down (%)	5.3 (4.9)

RESULTS

Baseline characteristics

The baseline characteristics of the patients with COPD and healthy volunteers are shown in table 1.

Evaluation 1: Relationship between leg and whole body activity in patients with COPD

Fourteen subjects were studied and all completed 2 days of recording with the Actiwatch. However, Dynaport

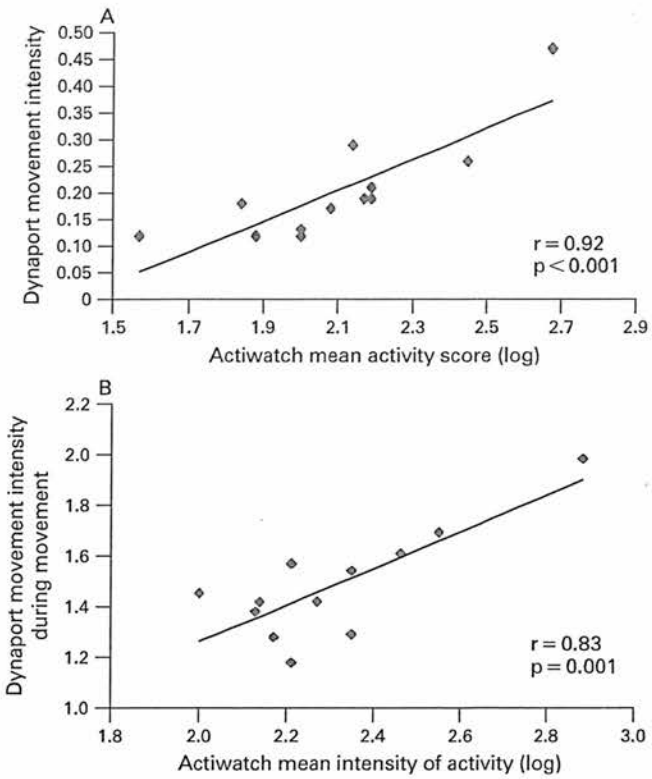

Figure 1 (A) Relationship between measures of mean activity by Dynaport and Actiwatch devices. (B) Relationship between measures of intensity of activity by Dynaport and Actiwatch devices.

measurements were unsuccessful in two patients owing to unrecognised lack of battery power (both patients) plus incorrect operation of the device by one patient. Simultaneously recorded data were therefore available in 12 patients with a mean recording duration of 18.7 (1.5) h.

Mean data for the activity outcomes and body position are shown in table 2. There was good agreement between the mean leg activity score recorded by the Actiwatch and the mean whole body activity level recorded by the Dynaport device (table 3 and fig 1A), and also between Actiwatch mean intensity of activity and all Dynaport activity assessments (table 3 and fig 1B). No relationship was seen between the time spent in specific positions and the activity levels assessed by the leg accelerometer. However, the mean number of counts recorded in each position for each patient was significantly different between sitting and walking (see table 1 in online data supplement).

Evaluation 2: Leg activity in patients with COPD and healthy volunteers

The patients and volunteers were of similar age and, by definition, differed in lung function (table 1). Quadriceps muscle strength was significantly less in the patients with COPD (difference 107 N, 95% CI 48 to 139; $p = 0.001$). The patients spent significantly less of the day mobile (difference 10.6%, 95% CI 3.1% to 18.2%; $p = 0.007$) and had a lower mean activity level (difference 61, 95% CI 27 to 96; $p = 0.001$) and lower intensity of activity score (difference 77, 95% CI 27 to 126; $p = 0.004$) than the healthy volunteers. Leg activity recordings were relatively stable between the days for both the patients with COPD and the volunteers. The mean (range) coefficient of variation was 21.6% (2.2–47.4%) for mean activity score, 15.7% (3.2–42%) for mean intensity of activity and 11.5% (1.5–31.3%) for percentage of time spent mobile. When different leg activity measures recorded in the patients with COPD were compared, mean activity scores were closely related to the mean intensity of activity ($r = 0.86$, 95% CI 0.73 to 0.93; $p<0.001$) with a weaker relationship between the mean activity score and the percentage of time scored as mobile ($r = 0.68$, 95% CI 0.44 to 0.83; $p<0.001$). However, the intensity of activity when exercising was not related to the amount of time spent mobile ($r = 0.27$, 95% CI −0.08 to 0.56; $p = 0.122$).

Evaluation 3a: Lower limb activity and laboratory assessments of exercise capacity

In this evaluation the Actiwatch accelerometer was worn for an average of 15.7 (0.2) h per day on each of the 3 days of recording. All functional measurements—lung mechanics, muscle strength, walking distance or self-completed questionnaires—were related to each other to a varying degree (see table 2 in online data supplement). There was a significant or near significant relationship between measures of leg activity and many of these variables (see table 3 in online data

Table 3 Correlation between different activity measures obtained from the Actiwatch and Dynaport Activity Monitor in 12 patients with chronic obstructive pulmonary disease (Evaluation 1)

	Actiwatch		
	Mean activity score	Mean intensity of activity score	Time spent mobile
Dynaport			
Time spent moving (%)	r = 0.83 95% CI 0.48 to 0.95 p = 0.001	r = 0.76 95% CI 0.32 to 0.93 p = 0.004	r = 0.48 95% CI −0.13 to 0.32 p = 0.118
Movement intensity	r = 0.92 95% CI 0.72 to 0.98 p<0.001	r = 0.88 95% CI 0.63 to 0.97 p<0.001	r = 0.35 95% CI −0.28 to 0.77 p = 0.27
Movement intensity during movement	r = 0.81 95% CI 0.45 to 0.95 p = 0.001	r = 0.83 95% CI 0.49 to 0.95 p = 0.001	r = 0.05 95% CI −0.54 to 0.61 p = 0.883
Time spent walking (%)	r = −0.42 95% CI −0.8 to 0.2 p = 0.171	r = −0.32 95% CI −0.76 to 0.31 p = 0.306	r = −0.42 95% CI −0.8 to 0.2 p = 0.169

Data recorded are Pearson's correlation coefficient, 95% confidence interval of the correlation and p value.

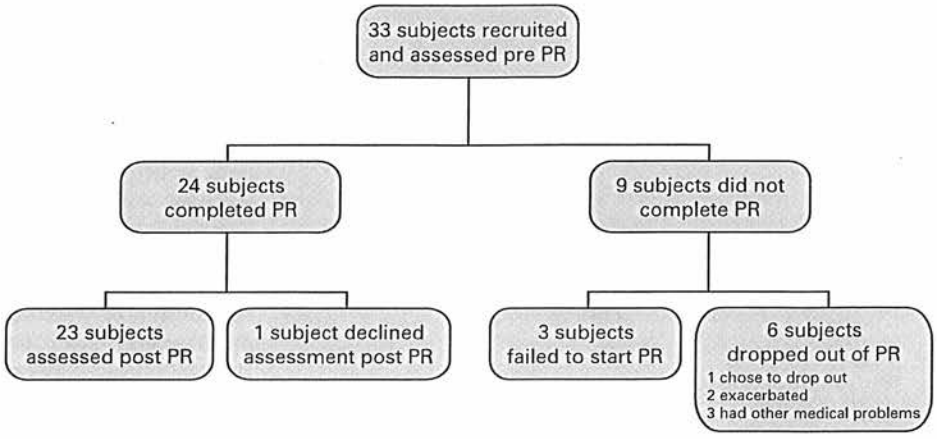

Figure 2 Flow chart showing the outcome for the 33 subjects referred to the pulmonary rehabilitation (PR) programme.

supplement). The mean activity of the legs and the percentage of time spent mobile were most closely related to absolute FEV_1 ($r = 0.57$, 95% CI 0.28 to 0.76; $p<0.001$ and $r = 0.51$, 95% CI 0.2 to 0.73; $p = 0.002$, respectively). There was a significant relationship between FEV_1 percent predicted and mean intensity of activity when exercising ($r = 0.5$, 95% CI 0.19 to 0.72; $p = 0.003$), although in this case the best univariate correlation was with TLCO ($r = 0.6$, 95% CI 0.25 to 0.81; $p = 0.003$). There was a weak relationship between mean leg activity and the subjective assessment of activity using the NEADL questionnaire ($r = 0.35$, 95% CI 0 to 0.62; $p = 0.049$).

Evaluation 3b: Lower limb activity and pulmonary rehabilitation

The number of patients participating in and completing the pulmonary rehabilitation programme is shown in fig 2. The change in outcome variables after completion of rehabilitation is presented in table 4. Subjects completing rehabilitation showed significant improvements in self-paced walking distance, quadriceps strength, breathlessness at rest and peak exercise, health status and level of anxiety and depression. In general, these changes exceeded the minimum clinically important difference and were paralleled by significant improvements in leg activity. However, the magnitude of change in walking distance and muscle strength were unrelated to the change in any index of leg activity.

Improvement in objectively measured leg activity was positively correlated with baseline FEV_1 ($r = 0.8$, 95% CI 0.58 to 0.91; $p<0.001$, fig 3). The only other baseline variables that contributed to the improvement in any measure of activity were 6 min walk distance and NEADL score. Baseline subjective activity level assessed using the NEADL questionnaire was related to change in the percentage of time spent mobile ($r = 0.56$, 95% CI 0.15 to 0.79; $p = 0.006$) and mean activity score ($r = 0.47$; 95% CI 0.08 to 0.71; $p = 0.021$) after completion of rehabilitation. Full details of the relationships between change in leg activity and baseline variables are shown in table 4 in the online supplement.

DISCUSSION

Exercise limitation in COPD integrates the effect of many different aspects of this condition including abnormal lung mechanics, peripheral muscle dysfunction and altered mood states. Subjective assessments of exercise limitation range from simple reporting of activity limited by dyspnoea such as the MRC dyspnoea scale[22] through to more global reporting of disability such as the SGRQ activity score or NEADL. Cardiopulmonary exercise testing can define the physiological limits to exercise, but this and other objective exercise tests define what the patient can do rather than what they actually do at home. In comparison, recording accelerometry provides

Table 4 Effect of pulmonary rehabilitation in the 23 subjects with chronic obstructive pulmonary disease who completed all assessments (Evaluation 3)

	Before PR	After PR	Mean (SE) difference after PR (95% CI)	p Value
Quadriceps MVC (N)	312 (20)	334 (23)	22 (31) (9 to 35)	0.002
6MWD (m)	274 (13)	333 (13)	59 (33) (45 to 73)	<0.001
Resting Borg score	1.6 (0.2)	0.9 (0.2)	0.7 (1.2) (0.2 to 1.6)	0.008
Peak Borg score	4.6 (0.2)	3.2 (0.3)	1.4 (1.7) (0.7 to 2.1)	<0.001
Leg activity				
% of time spent mobile	50.0 (2.7)	55.2 (2.6)	5.2 (9.4) (1.2 to 9.3)	0.014
Mean activity score ($\times 10^3$ counts/h)	81.5 (53.2)	117.2 (84.2)	35.7 (49) (14.5 to 56.9)	0.002
Mean intensity of activity score ($\times 10^3$ counts/h)	156 (69.2)	208.5 (123.4)	52.5 (74.2) (20.4 to 84.6)	0.001
Health status				
HAD Anxiety	7.2 (1)	5.6 (0.6)	1.6 (3.2) (0.2 to 3.0)	0.016
HAD Depression	6.4 (0.6)	4.4 (0.6)	2 (2.2) (1.0 to 2.9)	<0.001
SGRQ	62.9 (2.5)	47.8 (2.4)	15.1 (12.5) (8.9 to 19.7)	<0.001
NEADL	16.4 (0.5)	18.2 (0.5)	1.8 (1.7) (1.1 to 2.6)	<0.001

Data shown are mean (SE).
HAD, Hospital Anxiety and Depression questionnaire score; 6MWD, six minute walking distance (metres); MVC, maximum voluntary contraction; NEADL, Nottingham Extended Activities of Daily Living Questionnaire; PR, pulmonary rehabilitation; SGRQ, St George's Respiratory Questionnaire.

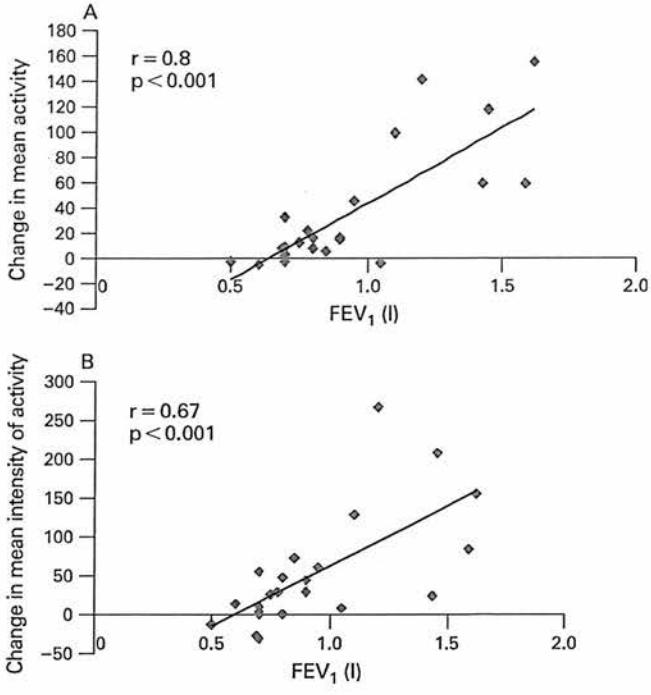

Figure 3 (A) Relationship between forced expiratory volume in 1 s (FEV_1) and change in Actiwatch leg mean activity after rehabilitation ($r = 0.8$, $p<0.001$). (B) Relationship between FEV_1 and change in Actiwatch leg mean intensity of activity after rehabilitation ($r = 0.67$, $p<0.001$).

insight into how much activity is undertaken. In this report we have focused on leg activity and confirm that this variable relates well to whole body activity, distinguishes patients with COPD from unaffected individuals and responds to rehabilitation. However, interpreting these data is not necessarily simple, nor do they simply track changes in the variables we usually report when assessing a response to treatment.

Leg activity monitoring showed modest day-to-day variability in patients with COPD and healthy volunteers comparable to that reported with other systems. There was good agreement between the activity scores of the Dynaport, a validated whole body accelerometer, and both the mean activity scores and mean intensity of activity scores of the leg device. The differences in daily leg activity of the healthy volunteers and the patients with COPD are comparable to those reported for whole body activity,[7] and improvements after rehabilitation suggest that leg actigraphy tracks other outcome measures and is responsive to intervention. The lack of agreement between leg activity and position monitoring data with the Dynaport system probably reflects the strict scoring standards we used to define mobility. However, we cannot exclude an effect due to leg movements when seated or lying. The lack of complete agreement between the two methods means that lower limb activity monitors cannot be substituted for those measuring total activity when determining whole body energy expenditure.[23] Despite this, lower limb activity is clearly the major determinant of whole body activity and, in most circumstances, lower limb measurement is likely to be an acceptable surrogate for a whole body system.

Of the three leg accelerometric variables we reported, mean activity provided an acceptable compromise between both the percentage of time spent immobile and the mean intensity of activity during exercise. These latter variables were unrelated in the patients with COPD, which suggests that the amount of time spent sitting or lying completely still was determined by different factors from those determining intensity of lower limb activity when exercise had to be undertaken. This was reflected to a degree in the relative lack of relationship between lower limb activity and conventionally used performance indicators such as walking distance, quadriceps strength and activity questionnaires. Although these variables were related, the major factor determining leg activity was FEV_1; patients with better lung function undertook a greater degree of activity. The relationship between lung function and walking distance was much weaker, albeit not dissimilar to published data,[2] as was the relationship between activity and walking distance. Hence, level of activity does not appear simply to reflect capacity but may be affected by lifestyle and choice. The subjectively reported limitation in activity of daily living score was weakly related to mean level of activity, and similar associations were seen with other subjective scores. However, unlike objective activity measures, subjective scores did not relate to measures of pulmonary function. These data suggest that level and extent of activity at home are independent measures of function which can only be approximately assessed using currently available laboratory physiological outcomes or activity questionnaires.

Pulmonary rehabilitation produced significant improvements in health status, lower limb muscle strength and exercise performance that are comparable to the best results reported with other programmes.[24] Significant improvement was seen in all measures of lower limb activity although, even after pulmonary rehabilitation, leg activity was still significantly less than that in age-matched controls. The magnitude of improvement in measures of functional capacity—such as walking distance and quadriceps strength—did not predict the change in leg activity at home, even though both were significantly greater after rehabilitation.

We initially hypothesised that the most inactive subjects would have a greater capacity to improve their level of activity after rehabilitation. In fact, the baseline level of activity was only weakly related to the improvement after rehabilitation, which suggests that even active individuals can further increase their level of activity with an effective rehabilitation programme. Instead, change in leg activity after rehabilitation, however expressed, was primarily influenced by lung function, although the pre-rehabilitation 6 min walking distance also made an independent contribution. Individuals with better exercise capacity and lung function thus did more at home and with greater intensity after completing rehabilitation. This is compatible with the subjective improvement in activity of daily living. As in previously published reports,[25] patients with a better preserved FEV_1 but worse perception of activity reported the greatest subjective benefit. The importance of spirometry as a predictor of outcome after rehabilitation is not entirely surprising as previous reports have highlighted the role of ventilatory capacity in determining improvement in walking distance after rehabilitation.[26–28]

The Actiwatch device was to be easy to use, acceptable to patients and had a low failure rate. As a simple strap-mounted device, it could be worn under clothing and, with a long battery life, it could be worn overnight and only needed to be removed for bathing. In contrast, the Dynaport was technically more difficult to use and, although light in weight, it was larger and noticeable. It includes both a waist and a leg strap and hence has to be removed overnight and during washing. The start-up procedure needs to be completed each morning and ideally both

batteries and memory card should be changed daily. In choosing an activity monitor, the ease of use of the Actiwatch has to be balanced against the more precise body position activity data obtained with the Dynaport.

Our data provide further support for the usefulness of monitoring daily activity at home in patients with COPD and confirm that simple monitoring of leg movement gives useful insights into daily activity. The intensity and amount of leg activity a patient undertakes at home gives rather different results from those predicted by more conventional measurements such as walking distance, muscle strength and health status questionnaires. Understanding why people improve some forms of activity but not others after treatment and what determines how much of their improved exercise capacity they use after rehabilitation is an important area of future research which will be greatly aided by the availability of valid monitoring methods such as actigraphy.

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Lower limb activity and its determinants in COPD

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Cardiovascular events in patients with COPD: TORCH Study results

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► Supplementary tables are published online only. To view these files please visit the journal online (http://thorax.bmj.com).

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ABSTRACT

Background Previous studies have suggested that long-term use of β agonists to treat chronic obstructive pulmonary disease (COPD) may increase the risk of cardiovascular adverse events. In this post hoc analysis, data from the TOwards a Revolution in COPD Health (TORCH) study were used to investigate whether use of the long-acting β_2 agonist salmeterol over 3 years increased the risk of cardiovascular adverse events in patients with moderate to severe COPD.

Methods TORCH was a randomised, double-blind, placebo controlled study conducted at 444 centres in 42 countries. Patients (n=6184; safety population) received twice daily combined salmeterol 50 μg plus fluticasone propionate 500 μg (SFC), either component alone, or placebo. Adverse events were recorded every 12 weeks for 3 years.

Results The probability of having a cardiovascular adverse event by 3 years was 24.2% for placebo, 22.7% for salmeterol, 24.3% for fluticasone propionate and 20.8% for SFC. Although a history of myocardial infarction doubled the probability of cardiovascular adverse events, the event rates remained similar across treatment groups.

Conclusion Post hoc analysis of the 3-year TORCH dataset showed that salmeterol alone or in combination (SFC) did not increase the risk of cardiovascular events in patients with moderate to severe COPD.

Chronic obstructive pulmonary disease (COPD) is now recognised as being a highly prevalent condition[1] that causes significant morbidity and mortality,[2] and commonly coexists with cardiovascular disease.[3] Cardiovascular events are one of the leading causes of mortality and hospitalisation in patients with COPD, particularly in those with mild to moderate disease.[4 5] Moreover, COPD is a strong risk factor for cardiovascular events, independent of smoking,[3 6 7] and impaired lung function is an important marker for cardiovascular mortality.[8 9] However, it is unclear whether COPD interventions other than smoking cessation[4] can modify the increased cardiovascular risk associated with COPD.

Recently there has been concern that the long-term use of inhaled bronchodilators commonly used in the treatment of COPD, including long-acting β_2 agonist (LABA) and anticholinergic drugs, may increase the risk of cardiovascular complications.[10–14] However, prospective data about the relative risk of therapy in patients with sufficient symptoms to be offered treatment with these drugs has, until recently, been lacking.

While the 3-year TOwards a Revolution in COPD Health (TORCH) study primarily investigated the effect of combination therapy with the LABA salmeterol (SAL) and the inhaled corticosteroid fluticasone propionate (FP) compared with placebo on all-cause mortality, other efficacy outcomes and adverse events (AEs) were also measured. The primary paper including the mortality analysis has already been published.[15] It reported that long-term use of SAL or the SAL plus FP combination (SFC) did not increase the rate of cardiac death. In view of the continuing concerns about cardiovascular safety in COPD therapy, we extended this analysis (post hoc) to consider the occurrence of cardiovascular AEs and serious adverse events (SAEs) in the TORCH study. We also explored the factors that might determine the incidence of cardiovascular events in these patients. Some of these results have previously been presented in abstract form.[16]

METHODS

Patients

Details of patient eligibility and study entry criteria have been published previously.[15] Eligible patients were current or former smokers aged 40–80 years with a prebronchodilator forced expiratory volume in 1 s (FEV_1) <60% of the predicted value and a ratio of prebronchodilator FEV_1 to forced vital capacity (FVC) of ≤0.70. The only exclusion criterion with respect to comorbidities was that subjects were considered unlikely to die of something other than COPD in the subsequent 3 years.

Design overview

The study design has been described in detail previously.[15 17] TORCH was a multicentre, randomised, double-blind, parallel-group, placebo controlled study conducted at 444 centres in 42 countries. After a 2-week run-in period, eligible patients were stratified by smoking status and randomised to receive either SFC 50/500 μg, SAL 50 μg, FP 500 μg or placebo twice daily for 3 years via a Diskus/Accuhaler inhaler (GlaxoSmithKline, Greenford, UK). Full details of the randomisation procedure have been reported elsewhere.[15 17]

The primary efficacy end point of the TORCH study was all-cause mortality. Other end points were rate of COPD exacerbations, health-related quality of life, lung function and AEs. After randomisation, patient visits occurred every 12 weeks to record any AE. At each visit the subject was allowed to spontaneously mention any

problems, then the investigator asked the following standard questions: (1) 'Have you had any (other) medical problems since your last visit/assessment?' and (2) 'Have you taken any new medicines other than those given to you within this study since your last visit/assessment?' An AE was defined as any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of the blinded study product, whether or not it was considered to be related to that product.

SAEs were those that resulted in any of the following outcomes: (1) death; (2) an immediate risk of death; (3) hospitalisation or prolongation of an existing hospitalisation; or (4) any other important medical event which, in the opinion of the investigator, jeopardised the subject's health. An independent safety and efficacy data monitoring committee performed safety reviews of all SAEs every 6 months. Causes of death were independently adjudicated in a standardised fashion by a clinical end point committee.[18]

Cardiovascular safety evaluation

Cardiovascular AEs were classified based on the Medical Dictionary for Regulatory Activities (MedDRA) Version 8.1 terms. MedDRA is the AE classification dictionary endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). All events in the cardiac disorders system organ class plus selected events from the vascular disorders and nervous system disorders system organ classes were included (table 1). Further analysis was also conducted on the subset of ischaemic events and on events related to stroke (table 1). No specific information was collected about whether patient-reported AEs had been objectively verified.

Subjects receiving medications commonly used to treat cardiovascular disease were identified; these medications were selected from dictionary groupings (listed in table 1).

Statistical analysis

The study was powered for its primary all-cause mortality end point and was not formally powered to detect differences in numbers of AEs between treatments.

Table 1 List of MedDRA system organ class (SOC) high-level group terms (HLGT) used for analysis of cardiovascular events, ischaemic cardiovascular events and stroke events, and list of cardiovascular medications included in the analysis

Cardiovascular events	**Ischaemic events**
► Cardiac disorders (SOC)	► Ischaemic coronary artery disorders
– Coronary artery disorders	► Coronary artery disorders NEC
– Cardiac arrhythmias	► Heart failures NEC
– Heart failures	► Right ventricular failures
– Cardiac disorder signs and symptoms	► Left ventricular failures
– Myocardial disorders	► Cardiomyopathies
– Cardiac valve disorders	► Pericardial disorders NEC
– Pericardial disorders	► Non-infectious pericarditis
► Nervous system disorders (SOC)	**Stroke events**
– Central nervous system vascular disorders	► Central nervous system vascular disorders (HLGT)
► Vascular disorders (SOC)	
– Arteriosclerosis, stenosis, vascular insufficiency and necrosis	
– Aneurysms and artery dissections	
– Embolism and thrombosis	
Cardiovascular medications	
► ACE inhibitors	► Antiarrythmics
► Angiotensin II antagonists	► Cardiac glycosides
► Antihypertensives	► Adrenergic and dopaminergic agents
► Beta blockers	► Organic nitrates
► Calcium channel blockers	

NEC, not elsewhere classified.

The safety population included all patients who took at least one dose of study medication. The number and proportion of patients reporting a cardiovascular AE over the 3 years were summarised by treatment group. To correct for differential treatment exposure between the treatments, the rate of cardiac events per 1000 treatment years was calculated by dividing the total number of AEs by the total number of years patients were exposed to study treatment, then multiplying by 1000. On-treatment deaths were defined as any death occurring up to 14 days after patients stopped their study medication.

The time to first cardiovascular AE was compared between treatment groups using Kaplan–Meier estimates and the log-rank test, stratified by smoking status; Kaplan–Meier cumulative incidence curves were also generated. Statistical significance was set at $p<0.05$.

RESULTS

Study population

Of 8554 patients with COPD recruited, 6184 were randomised and evaluated for safety (figure 1). This included 72 patients from five sites excluded from the published efficacy analyses.[15] One subject was randomised to placebo but took FP for the majority of the treatment period and was analysed with the FP group.

Demographic and baseline patient characteristics were balanced across treatment groups (table 2). The mean age was 65 years, 76% were male, mean smoking history was 48 pack-years and baseline postbronchodilator FEV_1 was 44% of predicted. At baseline, 7% of patients reported a history of previous myocardial infarction (MI), 41% were taking cardiovascular medications and 60% were taking short-acting anticholinergic drugs. Use of the long-acting anticholinergic tiotropium bromide during the study was low (3%) and was similar across treatment groups. Of the 187 subjects receiving tiotropium, over half took it for 12 weeks or less.

The proportion of patients who withdrew from the study was highest in the placebo group (44%) and lowest in the SFC group (34%) (SAL 37%, FP 39%). The total number of patient-years of exposure to the study drugs was 3278 for placebo, 3531 for SAL, 3555 for FP and 3700 for SFC.

Cardiovascular AEs

The proportion of patients who experienced a cardiovascular AE or cardiovascular SAE during the study was similar across treatment groups (17–20% and 10–12%, respectively) (table 3). When expressed as the number of events per 1000 treatment years, the rate of cardiovascular AEs was 142 in the placebo group and 110 in the SFC group. The probability of patients having a cardiovascular AE by 3 years was lowest for SFC at 20.8% (24.2% for placebo, 22.7% for SAL and 24.3% for FP; figure 2A; table 3). The probability of patients having a cardiovascular SAE by 3 years was lowest for SFC at 12.5% (15.4% for placebo, 13.6% for SAL and 14.7% for FP; table 3).

The proportion of patients experiencing an ischaemic cardiovascular AE was similar across treatment groups (9–11%; table 4). The rate of ischaemic cardiovascular AEs per 1000 treatment years was 68 for placebo, 70 for SAL, 62 for FP and 54 for SFC. The probability of patients having an ischaemic cardiovascular AE by 3 years was lowest for SFC at 11.3%, 14.6% for placebo, 13.4% for SAL and 13.8% for FP (figure 2B and table 4).

The proportion of patients with a stroke-related AE over the 3-year course of the study was similar in each treatment group (3% placebo, 2% SAL, 3% FP and 3% SFC). The rate of

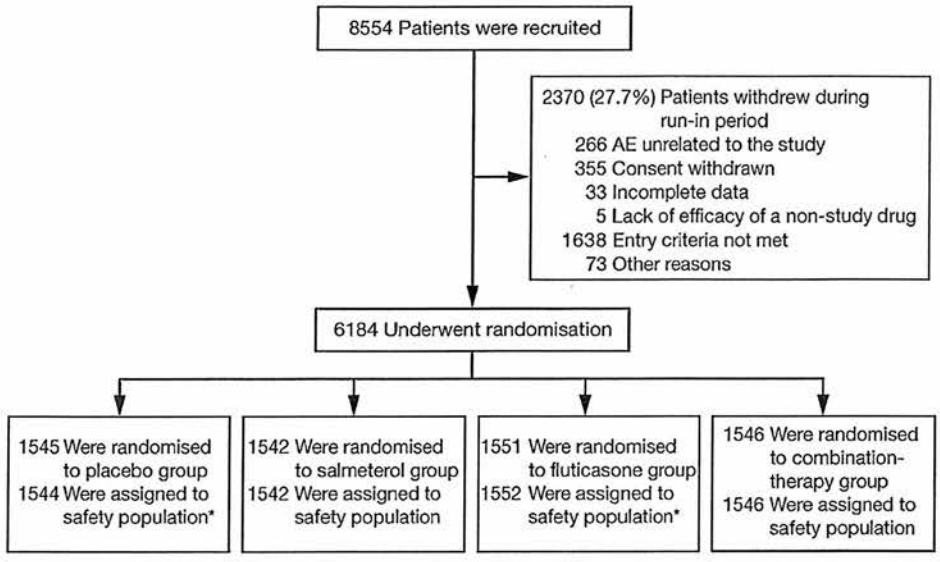

Figure 1 Patient flow. *The number of patients who underwent randomisation and the number of those included in the safety population differ in the placebo group and the fluticasone propionate group because one patient who was assigned to placebo received fluticasone propionate for more than half the study period; this patient was therefore included in the fluticasone propionate group for the safety analysis. AE, adverse event.

stroke-related AEs per 1000 treatment years was 17 for placebo, 13 for SAL, 16 for FP and 12 for SFC.

The likelihood of experiencing a cardiovascular AE was unaffected by gender and current smoking status (table 5). Patients who were on cardiovascular medications at baseline (figure 3), reported a previous MI (figure 4), were older or had lower baseline FEV_1 (table 5) had a higher probability of having a cardiovascular AE. There were no significant differences between treatments in the likelihood of an event being reported, nor was there consistent evidence for an interaction between treatment and spirometrically-defined disease severity with respect to cardiac events (see table 1 in online supplement) . In patients who had previously had an MI, the likelihood of having a cardiovascular event over 3 years was 54.4% on salmeterol compared with 49.1% with placebo (p =0.51) and 44.1% with SFC (p=0.051 relative to salmeterol (figure 4B and table 5).

Table 2 Patient demographic and baseline characteristics of the safety population

Variable	Placebo (n=1544)	Salmeterol (n =1542)	FP (n =1552)	SFC (n =1546)
Age at enrolment, years	65.1 (8.1)	65.2 (8.2)	65.1 (8.4)	65.0 (8.3)
Male gender, n (%)	1175 (76)	1176 (76)	1169 (75)	1164 (75)
Body mass index, kg/m^2	25.5 (5.2)	25.4 (5.2)	25.3 (5.1)	25.4 (5.3)
Postbronchodilator FEV_1, % predicted	44.1 (12.2)	43.6 (12.6)	44.1 (12.3)	44.3 (12.4)
<30%, n (%)	215 (14)	261 (17)	223 (14)	246 (16)
30—< 50%, n (%)	786 (51)	750 (49)	785 (51)	735 (48)
≥50%, n (%)	543 (35)	531 (34)	544 (35)	565 (37)
Geographical region, n (%)				
USA	348 (23)	351 (23)	350 (23)	352 (23)
Asia Pacific	188 (12)	189 (12)	193 (12)	188 (12)
Eastern Europe	297 (19)	296 (19)	293 (19)	293 (19)
Western Europe	478 (31)	475 (31)	481 (31)	477 (31)
Other	234 (15)	231 (15)	234 (15)	236 (15)
Current smoker, n (%)	664 (43)	657 (43)	666 (43)	667 (43)
Pack-years smoked	48.6 (27.0)	49.3 (27.7)	49.2 (28.5)	46.9 (26.5)
Previous COPD treatment, n (%)*				
ICS alone	346 (22)	278 (18)	310 (20)	295 (19)
LABA alone	118 (8)	138 (9)	133 (9)	137 (9)
ICS + LABA	453 (29)	417 (27)	416 (27)	437 (28)
Neither ICS nor LABA	557 (36)	634 (41)	629 (41)	623 (40)
Previous MI, n (%)	n=1543	n=1541	n=1552	n=1545
0	1432 (93)	1427 (93)	1460 (94)	1443 (93)
1	91 (6)	93 (6)	79 (5)	83 (5)
≥2	29 (1)	21 (1)	13 (<1)	19 (1)
Baseline CV treatment, n (%)†	608 (39%)	630 (41%)	630 (41%)	662 (43%)
Baseline short-acting anticholinergics, n (%)	926 (60%)	921 (60%)	943 (61%)	925 (60%)

Data are mean (SD) unless otherwise indicated.
CV, cardiovascular; FEV_1, forced expiratory volume in 1 s; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; MI, myocardial infarction; SFC, salmeterol/fluticasone propionate combination.
*Self-reported in the 12 months prior to screening.
†See list in table 1.

Table 3 Summary of all cardiovascular AEs and SAEs

	Placebo (n=1544)	Salmeterol (n=1542)	FP (n=1552)	SFC (n=1546)
All CV AEs				
Patients with CV AE, n (%)	281 (18)	287 (19)	306 (20)	267 (17)
Rate* of CV AE (no of events)	142 (466)	141 (496)	130 (462)	110 (405)
Probability† of CV AE by 3 years, %	24.2	22.7	24.3	20.8

	Hazard ratio	95% CI	p Value
SFC vs placebo	0.83	0.70 to 0.98	0.031
Salmeterol vs placebo	0.96	0.82 to 1.13	0.629
FP vs placebo	1.00	0.85 to 1.18	0.994

CV SAEs				
Patients with CV SAE, n (%)	176 (11)	168 (11)	180 (12)	160 (10)
Rate* of CV SAE (no of events)	75 (245)	66 (234)	66 (236)	57 (209)
Probability† of CV SAE by 3 years, %	15.4	13.6	14.7	12.5

	Hazard ratio	95% CI	p Value
SFC vs placebo	0.81	0.65 to 1.00	0.046
SAL vs placebo	0.89	0.72 to 1.10	0.268
FP vs placebo	0.94	0.76 to 1.15	0.542

*Rate=number of events per 1000 treatment years.
†Kaplan–Meier probability.
AEs, adverse events; CV, cardiovascular; FP, fluticasone propionate; SAEs, serious adverse events; SFC, salmeterol/fluticasone propionate combination.

However, the pattern of risk in other groups was inconsistent with salmeterol-treated patients having a similar incidence of events to patients treated with FP, as identified by their use of previous cardiac therapies (figure 3B). Patients who were taking short-acting anticholinergic treatment at baseline had a higher probability of cardiovascular events (table 5); however, these patients also had lower baseline percentage predicted FEV_1. The pattern of cardiovascular events was similar across treatment groups irrespective of baseline anticholinergic use.

Cardiovascular deaths

There were 882 deaths (14%) during the 3-year study period, including those both on and off study treatment (see table 2 in online supplement). Of these, 239 were due to cardiovascular causes as adjudicated by the clinical end point committee. For placebo, 71 deaths (4.6%) were due to cardiovascular causes compared with 45 (2.9%) for SAL, 61 (3.9%) for FP and 62 (4.0%) for SFC. There were 468 deaths while on treatment, of which 172 were due to cardiovascular causes. For placebo, 47 (3.0%) deaths were due to cardiovascular causes compared with 33 (2.1%) for SAL, 43 (2.8%) for FP and 49 (3.2%) for SFC.

DISCUSSION

COPD is not simply a lung disease[19] but is associated with an increased likelihood of complications outside the lungs. Support for this concept comes from recent studies that have shown significantly increased pulse wave velocity, independent of smoking status and other risk factors, in patients with stable COPD.[20] In these circumstances it is no surprise that cardiovascular morbidity and mortality is high in COPD.

Both β agonists and antimuscarinic agents, the main classes of bronchodilator drugs used to treat COPD, have the potential to precipitate cardiac rhythm disturbances and other cardiac events; however, this has not been regarded as important in clinical practice until recently. Unfortunately, unlike the situation for cardiovascular disease, most studies of drug treatment in COPD have been relatively brief (≤1 year) and have only reported on-treatment data. These studies have made the largest

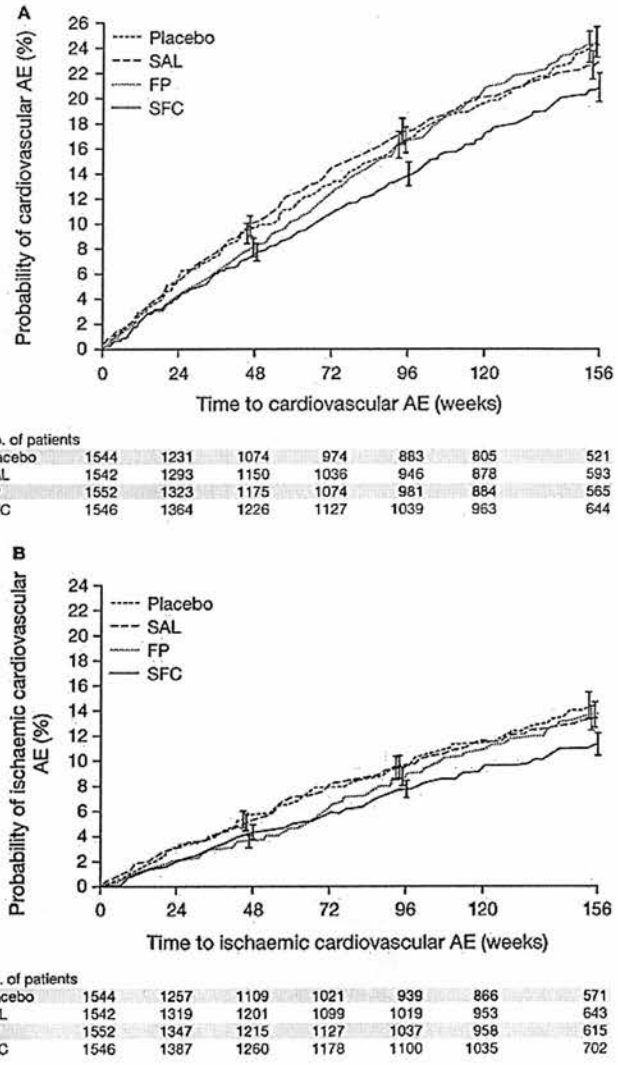

Figure 2 Cumulative incidence of (A) all cardiovascular adverse events and (B) ischaemic cardiovascular adverse events. Full details of the data presented in (A) and (B) including statistical testing are shown in tables 3 and 4, respectively. Vertical bars represent standard errors. AE, adverse event; FP, fluticasone propionate; SAL, salmeterol; SFC, salmeterol/fluticasone propionate combination.

contribution to the systematic reviews in this field, at least as far as patients receiving treatment for symptoms are concerned. As the TORCH study was conducted in a patient group likely to be prescribed inhaled LABAs, the TORCH dataset addresses some of the problems inherent in these earlier analyses. The current analysis provides generally reassuring results about the cardiovascular safety of inhaled LABA treatments in patients with COPD.

TORCH is the largest and longest prospective trial to examine the role of an inhaled LABA and an inhaled corticosteroid in COPD. Half of the >6000 patients were randomised to a regime containing SAL and, allowing for dropouts, this provides 7231 patient-years of exposure to these agents. Over the 3 years, approximately 1 in 5 patients experienced a cardiovascular AE. The event rate was lowest in those receiving SAL in combination with FP and not different from those patients treated with placebo or with LABA monotherapy. A SAE requiring hospitalisation and new cardiovascular ischaemic events were approximately half as common as the total cardiovascular event rate,

Table 4 Ischaemic cardiovascular AEs

	Placebo (n =1544)	Salmeterol (n =1542)	FP (n =1552)	SFC (n =1546)
Patients with ischaemic CV AE, n (%)	166 (11)	166 (11)	167 (11)	144 (9)
Rate* of ischaemic CV AE (no of events)	68 (224)	70 (240)	62 (222)	54 (199)
Probability† of ischaemic CV AE by 3 years, %	14.6	13.4	13.8	11.3

	Hazard ratio	95% CI	p Value
SFC vs placebo	0.76	0.61 to 0.95	0.016
Salmeterol vs placebo	0.93	0.75 to 1.16	0.531
FP vs placebo	0.93	0.75 to 1.15	0.477

*Rate=number of events per 1000 treatment years.
†Kaplan–Meier probability.
AEs, adverse events; CV, cardiovascular; FP, fluticasone propionate; SFC, salmeterol/fluticasone propionate combination.

but there was a similar pattern across treatment groups. Seven percent of patients had a history of previous MI. In this group the cardiovascular event rate, as would be expected, was higher. Again, no trend was seen for more AEs in those patients randomised to treatment with SAL in combination with FP. However, the data for SAL alone are inconclusive, possibly due to the small sample size in this smaller subgroup of patients.

Unlike other COPD studies, TORCH developed a rigorous methodology for determining the likely cause of death which was adjudicated by an expert panel blinded to the study medication.[18] Moreover, there was effectively complete follow-up of the vital status of all patients 3 years after randomisation. In this data set, the patients randomised to LABA alone had the lowest rate of cardiovascular death while those who received placebo had the largest number of events. The number of on-treatment deaths, analogous to data included in earlier COPD studies, showed a similar pattern across treatments.

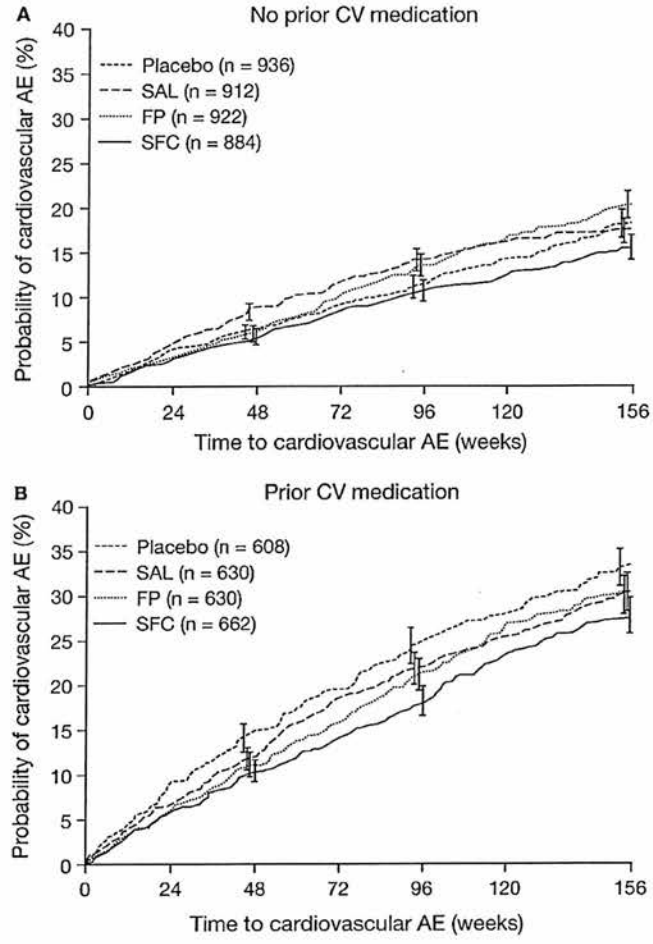

Figure 3 Cumulative incidence of all cardiovascular adverse events in patients who (A) did not receive or (B) did receive cardiovascular medication (listed in table 1) in the 12 months prior to screening. Full details of the data presented in this figure including statistical testing are shown in table 5. Vertical bars represent standard errors. AE, adverse event; CV, cardiovascular; FP, fluticasone propionate; SAL, salmeterol; SFC, salmeterol/fluticasone propionate combination.

Table 5 Kaplan–Meier probability of a cardiovascular adverse event by 3 years by subgroups

	N	Placebo (n=1544)	Salmeterol (n=1542)	FP (n=1552)	SFC (n=546)
Age					
<55	706	13.2	12.5	13.4	13.4
55–64	1988	20.2	18.8	20.7	17.4
65–74	2706	26.6	24.8	26.9	22.1
≥75	784	39.2	34.9	35.4	32.9
Sex					
Male	4684	24.4	23.0	24.0	20.7*
Female	1500	23.4	21.9	25.3	21.0
Smoking status					
Current	2654	22.2	22.0	22.4	20.5
Former	3530	25.8	23.3	25.9	20.9*
Baseline FEV_1					
<30%	945	25.8	32.1	26.7	23.5
30–<50%	3056	25.7	20.7	25.4	23.4
≥50%	2183	21.7	21.7	21.8	16.2*
Baseline CV treatment					
Yes	2530	33.5	30.3	30.4	27.9*
No	3654	18.3	17.6	20.2	15.4
Prior MI					
Yes	419	49.1	54.4	41.0	44.1
No	5762	22.2	20.2	23.3	19.1
Baseline short-acting anticholinergics					
Yes	3715	25.2	24.0	25.6	22.0
No	2469	22.7	21.0	22.4	18.9

*p<0.05 versus placebo.
CV, cardiovascular; FEV_1, forced expiratory volume in 1 s; FP, fluticasone propionate; MI, myocardial infarction; SFC, salmeterol/fluticasone propionate combination.

A range of predictable factors increases the cardiovascular event rate including higher age, a history of previous cardiac disease and worse lung function. None of these factors interacted with treatment to identify a specific 'at-risk' group. Somewhat surprisingly we saw no difference in event rate between current and ex-smokers, which may reflect our study entry criteria or possibly the nature of cardiovascular disease in patients with COPD. We did not control for the use of inhaled anticholinergic drugs although, when used, this was predominantly ipratropium as tiotropium was not available in most countries until TORCH was nearing completion. In those patients treated with an anticholinergic agent, there was a suggestion of a somewhat higher cardiovascular event rate but these patients also had lower baseline lung function. The association seen is therefore likely to represent the confounding influence of disease severity, an issue that has made interpretation of previous studies of COPD therapy particularly difficult. Patients in GOLD stage 4 receiving salmeterol appeared to have more cardiac events, although the

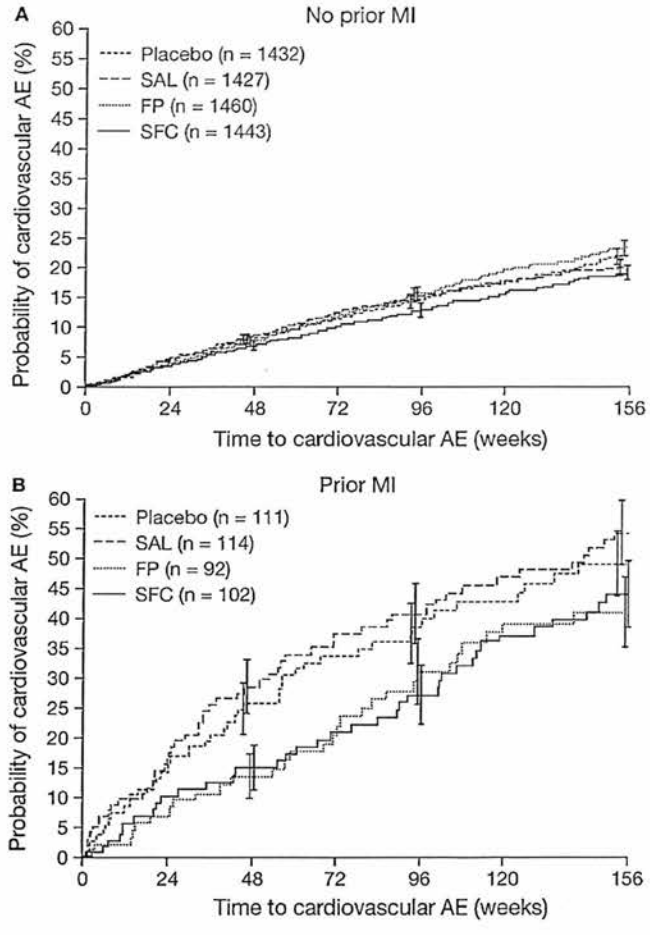

Figure 4 Cumulative incidence of all cardiovascular adverse events in patients who (A) had not experienced or (B) had experienced a myocardial infarction prior to study entry. Full details of the data presented in this figure including statistical testing are shown in table 5. Vertical bars represent standard errors. AE, adverse event; FP, fluticasone propionate; MI, myocardial infarction; SAL, salmeterol; SFC, salmeterol/fluticasone propionate combination.

differences between treatment groups were not significant. This finding is at odds with the lower than average reported incidence of events with salmeterol in GOLD stage 3 and probably reflects the lower sample size in the GOLD stage 4 population with correspondingly widened confidence intervals for these data.

Our study has strengths and some limitations. We monitored our patients regularly throughout the 3-year study, but events were self-reported rather than being in response to a predetermined diagnostic list. We did not undertake ECG or echocardiographic evaluations at the study outset and there was no requirement to provide objective documentation of the nature of any new cardiovascular episode. However, we did include patients with a history of cardiovascular disease provided it was not thought that this was the main cause for their symptoms or that they were likely to die from this during the study. This is an important difference from earlier studies where more restrictive eligibility criteria were applied. As in other large COPD studies, for example UPLIFT[21] and TRISTAN,[22] patients randomised to placebo tended to withdraw more frequently than those randomised to active therapy, probably reflecting their deteriorating condition. Thus, patients continuing in the placebo arm of our on-treatment analysis represent a relatively fitter group of patients with COPD. Despite this, we saw no suggestion that patients on treatment were more likely to experience adverse cardiovascular problems. Finally, we lack data about whether the use of these agents increases the risk of cardiovascular events during an acute exacerbation. Recent literature reviews have failed to report any association between use of high-dose β agonists and risk of arrhythmias in this setting.[23]

For some of our data the SFC combination appeared to be associated with important reductions in the incidence of adverse cardiovascular events. Although this difference may simply have been due to chance, other biologically plausible mechanisms exist which can account for this effect. It has been suggested that inflammation occurring in COPD might directly promote vascular damage[24] and this may be reduced when airway inflammation is decreased, as has been demonstrated with a LABA/inhaled steroid combination.[25] Our data cannot address this hypothesis, but this concept is supported by recent observations from a large database study that patients who used inhaled corticosteroids were less likely to experience cardiovascular deaths than those who received bronchodilators alone.[12] This is consistent with the general conclusions of the TORCH study that there was a reasonable (but not conclusive probability that combination treatment with SAL plus FP prolongs life in COPD. An alternative explanation for the effect of SFC on cardiovascular outcomes may be its relative efficiency in preventing exacerbations of COPD which are associated with elevations in troponin T and a raised cardiac infarction injury score, at least in hospitalised patients.[26 27] Further studies will be needed to address whether these potentially important mechanisms best explain the observed data.

In summary, in this large prospectively collected dataset, the occurrence of new cardiovascular AEs was no more frequent in patients treated with a LABA than in those treated with placebo. In addition, we saw some evidence that the combination of a LABA and an inhaled corticosteroid might offer a degree of cardioprotection. These data from patients with moderate to severe COPD provide reassurance that our current use of inhaled LABA therapies is not harmful to cardiovascular health.

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Competing interests PMAC has received consulting fees from AstraZeneca, GlaxoSmithKline, Nycomed and Pfizer; speaking fees from GlaxoSmithKline and Nycomed; and grant support from Boehringer-Ingelheim and GlaxoSmithKline. JAA, CC, LRW and JCY are employed by and hold stock in GlaxoSmithKline. BC has received consulting fees from Altana, AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline; speaking fees from Altana, AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline; and grant support from Boehringer-Ingelheim and GlaxoSmithKline. GTF has received consulting fees from Boehringer-Ingelheim, GlaxoSmithKline, Novartis and Schering Plough; speaking fees from Boehringer-Ingelheim, GlaxoSmithKline and Pfizer; and grant support from Altana, Boehringer-Ingelheim, Emphasys Medical Inc, Forrest, GlaxoSmithKline, Mannkind Corporation and Novartis. CJ has received consulting fees from Altana, AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline; speaking fees from Altana, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline and Novartis; and grant support from GlaxoSmithKline. PWJ has received consulting fees from AstraZeneca, GlaxoSmithKline, Novartis and Roche; speaking fees from AstraZeneca and GlaxoSmithKline; and grant support from Boehringer-Ingelheim and GlaxoSmithKline. JV has received consulting fees from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Hoffman-LaRoche and Nycomed; speaking fees from AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline; and grant support from GlaxoSmithKline.

Ethics approval The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent.

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Cardiovascular events in patients with COPD: TORCH Study results

Peter M A Calverley, Julie A Anderson, Bartolome Celli, et al.

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Reported Pneumonia in Patients With COPD : Findings From the INSPIRE Study

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Original Research

COPD

Reported Pneumonia in Patients With COPD

Findings From the INSPIRE Study

Peter M. A. Calverley, MB; Robert A. Stockley, MD, DSc; Terence A. R. Seemungal, PhD; Gerry Hagan, MD; Lisa R. Willits, MSc; John H. Riley, MD; and Jadwiga A. Wedzicha, MD; on behalf of the Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE) Investigators

Background: **Pneumonia is an important complication of COPD and is reported more often in patients receiving inhaled corticosteroids (ICSs). Little is known about the clinical course and factors predisposing to pneumonia in patients with COPD. We investigated patient characteristics and symptoms occurring before pneumonia reports in the Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE) study.**

Methods: **This was a 2-year, double-blind, double-dummy parallel study of 1,323 patients randomized to salmeterol/fluticasone propionate 50/500 μg bid (SFC) or tiotropium 18 μg once daily (Tio). Baseline demographics, including serum C-reactive protein (CRP) levels, were measured, and daily record cards (DRCs) were completed.**

Results: **We identified 87 pneumonia reports from adverse event records (SFC = 62; Tio = 25) in 74 patients (SFC = 50; Tio = 24), compared with 2,255 exacerbations (SFC = 1,185; Tio = 1,070). Pneumonia was more common in patients with severe dyspnea and in those with a baseline CRP level > 10 mg/L. Numbers of de novo pneumonias (events that were not preceded by symptoms of an exacerbation) were similar between treatment groups, but pneumonia was more likely after either a treated or untreated unresolved exacerbation in patients receiving ICSs (SFC = 32; Tio = 7). Similar results were seen when analysis was confined to radiologically confirmed events.**

Conclusions: **Pneumonia is much less frequent than exacerbation in COPD. The excess of events with ICS treatment appears to be associated with protracted symptomatic exacerbations. Earlier identification and treatment of these events to prevent pneumonia merits further investigation.**

Trial registry: **ClinicalTrials.gov; No.: NCT00361959; Study No.: SC040036; URL: clinicaltrials.gov**

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Abbreviations: BDI = baseline dyspnea index; CRP = C-reactive protein; DRC = daily record card; HCU = health-care use; HR = hazard ratio; ICS = inhaled corticosteroid; INSPIRE = Investigating New Standards for Prophylaxis in Reduction of Exacerbations; LABA = long-acting β-agonist; MRC = Medical Research Council; SFC = salmeterol/fluticasone propionate 50/500 μg bid; SGRQ = St. Georges Respiratory Questionnaire; Tio = tiotropium bromide 18 μg once daily; TORCH = Toward a Revolution in COPD Health

Pneumonia is the sixth leading cause of death and the leading cause of death from infectious disease.[1,2] Multiple sets of treatment guidelines for pneumonia exist,[3-5] and their implementation has significantly reduced morbidity and mortality of the disease.[6-8]

Patients with pneumonia commonly present with one or more symptoms, such as cough, fever, chills, fatigue, dyspnea, rigors, and pleuritic chest pain with or without respiratory signs. Chest radiograph enables a definitive diagnosis of pneumonia to be made, although guidance differs as to whether this investigation is mandatory.[9] The diagnosis of COPD exacerbations includes episodes in which cough, sputum, and breathlessness are major symptoms.[10] Without a chest radiograph, distinguishing between pneumonia and a COPD exacerbation can be difficult. Patients with COPD are at greater risk of developing

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pneumonia than the general population,[11,12] and patients with COPD who are hospitalized with pneumonia fare worse than patients without COPD.[13] A database review suggested that using inhaled corticosteroids (ICSs) increases the risk of hospitalization with pneumonia,[14] but this may be confounded by disease severity, as ICS/long-acting β-agonists (LABAs) are recommended for patients with recurrent exacerbations.[15] Two large prospective randomized controlled trials identified an increased risk of physician-reported pneumonia in patients receiving treatments containing the ICS fluticasone propionate.[16,17] This finding was confirmed using a lower dose of ICS[18,19] but was not seen in an analysis of trials using budesonide.[20] In the Toward a Revolution in COPD Health (TORCH) study, only limited information was available about the clinical course of the pneumonias reported.[21] In the Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE) study, patients recorded their symptoms on daily record cards (DRCs) throughout the 2-year study. This provided a unique opportunity to study the temporal relationship between common patient-reported respiratory symptoms and the occurrence of physician-reported pneumonia in a carefully characterized group of patients with COPD.

As hospitalization rates due to pneumonia did not differ in patients treated with placebo or bronchodilators alone,[16-19] we hypothesized that treatment with ICS would influence the type and duration of the symptoms preceding clinical diagnosis of pneumonia and that patients with pneumonia would differ in their baseline characteristics from those without pneumonia. To test these ideas, we reviewed patient DRCs to determine whether any distinctive patterns of symptoms were associated with pneumonia.

Materials and Methods

The study methodology and primary outcomes of the INSPIRE study have been published.[17,22] Patients were randomized to receive salmeterol plus fluticasone propionate 50/500 μg bid (SFC) or tiotropium bromide 18 μg once daily (Tio) in a 2-year, multicenter, double-blind, double-dummy parallel study.

Baseline measurements included age, sex, smoking status, FEV_1 (before and after 400 μg salbutamol), health status using the St. George's Respiratory Questionnaire (SGRQ),[23] modified Medical Research Council (MRC) breathlessness score, baseline dyspnea index (BDI),[24] prior exacerbation history, and prior ICS use. At randomization, FEV_1, SGRQ, and BDI were collected,[17] blood was taken, and CRP was measured in serum by Quest Diagnostics using a high-sensitivity nephelometry assay. Patients attended at 2 and 8 weeks postrandomization and then every 3 months for a total of 2 years. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Outcomes

No a priori definition of pneumonia existed in the study protocol and episodes were identified from adverse event reports of pneumonia (reported pneumonias), bronchopneumonia, and lobar pneumonia. Pneumonia reports defined as serious adverse events (those that were fatal, life threatening, or resulted in hospitalization) were reviewed by a physician to determine if a chest radiograph was used in the diagnosis and whether it confirmed the features of pneumonia. The start and resolution of a pneumonia event (ie, duration) was determined by the study-site investigator.

Daily Record Cards

Patients recorded increased symptoms of cough, breathlessness, colds, wheeze, and whether they had a fever and/or sore throat in the previous 24 h in their DRC. Sputum color and volume were scored as described previously.[25] A change in sputum color or volume was defined as an increase of at least one unit from baseline (median during run-in) with a minimum value of three for sputum color and one for sputum volume.

Symptom-defined exacerbations were determined using DRCs. These were identified as an acute worsening of two or more major symptoms (dyspnea, sputum volume, or purulence) or one major symptom and a minor symptom (sore throat, wheeze, colds, fever, increased cough) for at least 2 consecutive days.[10,26] Health-care use (HCU) exacerbations[15] were those treated by oral corticosteroids and/or antibiotics or those in which the patient was hospitalized. An untreated exacerbation was a symptom-defined exacerbation wherein the case report form showed no medical intervention. An exacerbation was considered resolved when associated symptoms returned to normal for 5 consecutive days. The day of resolution of the exacerbation was the day on which the last symptom of the exacerbation was stated in the DRC.

For all pneumonia reports, the DRC was analyzed for 35 days before and 21 days after diagnosis. Initially, the number of patients reporting an increase in a specific symptom on each day was plotted. Subsequently, the occurrence of a COPD exacerbation as defined above was related to the onset of the pneumonia event identified from the adverse event report. These data were reviewed in a random order by four physician members of the Steering Committee (P. M. A. C., R. A. S., T. A. R. S., J. A. W.) who were blinded to treatment allocation in order to define the relationship between symptom onset and the report of the pneumonia.

In this post hoc analysis, two complementary approaches to classifying the progression of events were adopted: a rule-based approach or a pattern-based approach. The rule-based approach involved the independent application of one of three prespecified definitions of the events preceding a pneumonia diagnosis:

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pneumonia following HCU exacerbation, pneumonia following an untreated exacerbation, or de novo pneumonia (few symptoms before the event onset and no prior exacerbation).

Discrepant categorizations between physicians were reviewed jointly and a consensus reached. Full definitions for the rule-based approach and a description of the pattern-based approach, which was used to further characterize the prodrome, are presented in e-Appendix 1.

Statistical Analysis

The time to first pneumonia was compared between treatments using a Cox proportional hazards analysis adjusted for smoking status, age, sex, disease severity (% predicted FEV_1), and country. The effect of different baseline predictors of pneumonia was investigated using the same model adjusted for treatment, smoking status, age, sex, disease severity, and country, with additional covariates of previous exacerbation history, BMI, baseline SGRQ total score, modified MRC score, baseline dyspnea index score, and CRP. Kaplan-Meier plots were generated for time to first pneumonia event and for three predefined ranges of baseline CRP.[27] The effects of different predictors of pneumonia were summarized by hazard ratios (HRs) and 95% CI. No formal statistical analysis was conducted for the descriptive data relating symptoms to pneumonia diagnosis.

Table 1—*Number of Patients with Reported Pneumonia Events*

Pneumonia Events	SFC (n = 658)	Tio (n = 665)
All pneumonia		
Patients	50 (8)	24 (4)
Events[a]	62	25
Serious pneumonia		
Patients	41 (6)	19 (3)
Events[a]	52	19
Fatal pneumonia		
Patients	3 (<1)	0
Events	3	0
All pneumonia	62	25
Duration, mean (SD), d	19.4 (19.8)	23.0 (21.7)
<1 wk	4 (6)	0
1 to <2 wk	26 (42)	9 (36)
2 to <3 wk	15 (24)	10 (40)
3 to <4 wk	5 (8)	1 (4)
≥4 wk	12 (19)	5 (20)

Data are expressed as No. (%) unless otherwise noted. SFC = salmeterol/fluticasone propionate 50/500 μg bid; Tio = tiotropium bromide 18 μg once daily.

[a]Patients can have more than one event.

Results

In the 1,930 patient-years of evaluable postrandomization data there were 2,255 HCU exacerbations (1,185 SFC; 1,070 Tio) and 5,152 symptom-defined events (2,720 SFC; 2,432 Tio). Pneumonia events were reported by 74 patients on 87 occasions (SFC: 50 patients, 62 events; Tio: 24 patients, 25 events (Fig 1, Table 1). The estimated on-treatment probability of having pneumonia by 2 years was 9.4% in the SFC arm and 4.9% in the Tio arm. The HR for time to first pneumonia was 1.94 (95% CI, 1.19-3.17) for SFC vs Tio ($P = .008$) (Fig 2). Restricting the analysis to the 50 radiographically confirmed events did not change this conclusion (HR, 1.98%; 95% CI, 1.04-3.76; $P = .037$).

Of the 87 reported pneumonias, 71 episodes in 60 patients were identified as serious adverse events (SFC: 41 patients; Tio: 19). A chest radiograph was performed for 64 (90%) serious events, and 50 showed the presence of infiltrates, consistent with the diagnosis of pneumonia. Three patients in the SFC arm who were hospitalized with pneumonia died.

The duration of all reported pneumonias is summarized in Table 1. Within the first 2 weeks, 48% of SFC-reported and 36% of Tio-reported pneumonias resolved. Approximately 20% of reported pneumonias in both treatment arms took ≥4 weeks to resolve.

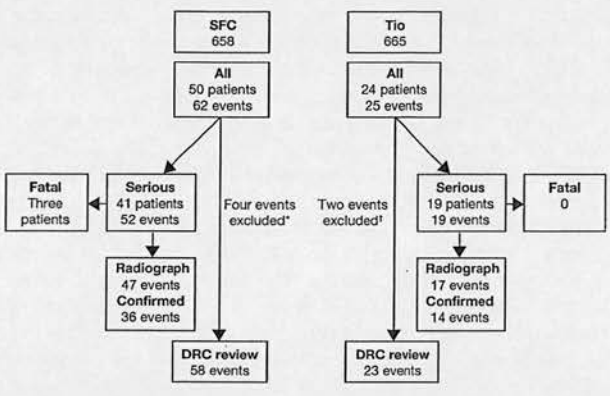

FIGURE 1. Reported pneumonia events in the Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE) Study (Consolidated Standards of Reporting Trials [CONSORT] diagram). *Three events within 1 week of randomization; one event excluded as within 2 weeks of another event. †Two events within 1 week of randomization. DRC = daily record card; SFC = salmeterol/fluticasone propionate 50/500 μg bid; Tio = tiotropium 18 μg once daily.

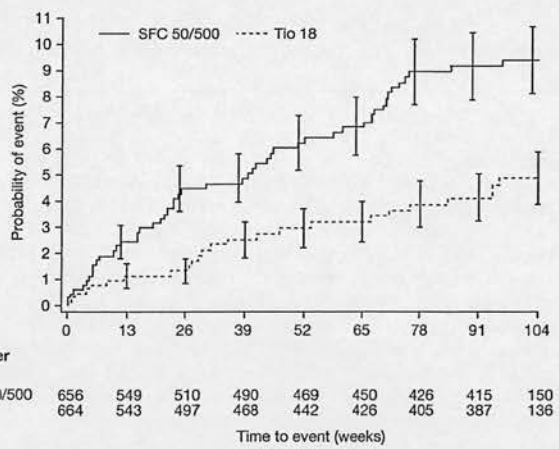

FIGURE 2. Time to first pneumonia. See Figure 1 legend for expansion of abbreviations.

Table 2—*Review of Symptoms*

Pneumonia Events	SFC (n = 658)	Tio (n = 665)
Total, self-reported (radiographically confirmed)	58 (34)	23 (13)
Rule classification		
De novo	22 (10)	16 (10)
HCU exac	16 (11)	3 (2)
Untreated exac	20 (13)	4 (1)
Pattern classification		
De novo	15 (7)	11 (7)
Resolved HCU exac	4 (1)	0 (0)
Resolved untreated exac	2 (0)	3 (0)
Unresolved HCU exac	17 (12)	4 (2)
Unresolved untreated exac	15 (11)	3 (2)
Insufficient data	5 (3)	2 (2)

A total of 47 radiologically confirmed events are included (numbers in parentheses), as three events confirmed as being pneumonic in nature occurred within 7 days of randomization and were believed unlikely to be related to randomized therapy. Exac = exacerbation; HCU = healthcare use. See Table 1 legend for expansion of other abbreviations.

Symptoms Associated With Pneumonia Events

A general increase in patient symptoms prior to a reported pneumonia was observed independent of treatment arm. There was an increase in reported sputum volume and cold symptoms at pneumonia onset with SFC, whereas fever was more common in pneumonias in the Tio group (e-Figure 1).

Exacerbations and Pneumonia

DRC completion rate was 98% overall, 91% in the 5 weeks before a pneumonia diagnosis and 70% during the reported pneumonia. Five reported pneumonias occurring within 1 week of randomization (SFC = 3; Tio = 2) and two reports in one patient within 5 days of each other (SFC) were considered a single event and were excluded. This left 81 reported pneumonias for further characterization, although seven (9%) had insufficient DRC data for characterization using the pattern-based approach. e-Figure 2 shows examples of the DRC data in three pneumonia categories using the rule-based approach. This analysis (Table 2) identified 22 and 16 de novo reported pneumonias in the SFC and Tio arms, respectively, 16 HCU exacerbations that preceded the reported pneumonias in the SFC group (7 antibiotic treated; 1 corticosteroid treated; 8 both) and 3 in the Tio group (1 of each treatment group). Similarly, 20 untreated exacerbations preceded reports of pneumonia in the SFC group vs 4 in the Tio group. Pattern-based approach results were consistent with those of the rule-based approach. When this analysis was confined to events in which there was known radiologic abnormality and which occurred more than 7 days after randomization to trial treatment (Table 2), an even clearer picture emerged with identical numbers of de novo events in each group but more unresolved exacerbations among pneumonias in the SFC-treated patients.

Predictors of the Risk of Pneumonia in Patients With COPD

The baseline demographics of the treatment groups were similar irrespective of the subsequent occurrence of pneumonia (Table 3). Table 4 summarizes the frequency of reported pneumonia by different subgroups. Among 550 patients from Eastern Europe, 41 (8%) had at least one pneumonia reported, compared with 33 (4%) of 773 patients from Western Europe.

Covariate analyses (Table 5) showed pneumonia was significantly more likely in patients with baseline CRP > 10 mg/L vs < 3 mg/L ($P = .004$), a difference that became more apparent over time (Fig 3). After adjustment for other predictive factors, patients with a BDI of 0 to 4 had an estimated increased risk of pneumonia at any time during the 2-year study of 131%

Table 3—*Baseline Characteristics of Patients with Pneumonia Events*

Characteristic	Pneumonia		No Pneumonia	
	SFC (n = 50)	Tio (n = 24)	SFC (n = 608)	Tio (n = 641)
Age, y	64 (8)	68 (6)	64 (8)	64 (8)
Men, %	86	96	81	83
BMI, kg/m^2	25 (4)	25 (7)	26 (5)	25 (5)
Current smokers, %	28	50	38	38
Prebronchodilator FEV_1,[a] L	1.03 (0.25)	1.16 (0.31)	1.05 (0.30)	1.06 (0.31)
Postbronchodilator FEV_1,[a] L	1.12 (0.27)	1.21 (0.27)	1.11 (0.30)	1.13 (0.31)
Postbronchodilator FEV_1, % predicted[a]	37 (8)	41 (7)	39 (8)	39 (9)
SGRQ total score[a]	53 (16)	58 (14)	50 (18)	52 (17)
Prior ICS use, %	52	38	48	52
Patients with at least one exacerbation in previous 12 mo, %	92	92	85	88
Patients with at least one moderate/severe exacerbation in previous 12 mo, %	74	75	72	73

Data are expressed as mean (SD) unless otherwise noted. ICS = inhaled corticosteroid; SGRQ = St. George's Respiratory Questionnaire. See Table 1 legend for expansion of other abbreviations.
[a]Taken at screening.

Table 4—*Patients With Pneumonia Events by Subgroup*

Subgroup	SFC (n = 658)	Tio (n = 665)
Region		
Western Europe	23/384 (6)	10/389 (3)
Eastern Europe	27/274 (10)	14/276 (5)
Smoking status		
Current	14/247 (6)	11/254 (4)
Former	36/411 (9)	12/411 (3)
Age		
≤65	22/311 (7)	8/315 (3)
>65	28/347 (8)	16/350 (5)
Sex		
Male	43/533 (8)	22/556 (4)
Female	7/125 (6)	1/109 (<1)
% Predicted FEV_1 at screening		
<30%	11/100 (11)	2/103 (2)
≥30%	39/558 (7)	22/562 (4)
Prior exacerbation		
0	13/182 (7)	6/182 (3)
1	14/196 (7)	9/193 (5)
≥2	23/280 (8)	9/290 (3)
BMI		
<20	3/75 (4)	2/69 (3)
20 to <25	23/244 (9)	17/271 (6)
25 to <29	13/206 (6)	3/185 (2)
≥29	11/133 (8)	1/140 (<1)
SGRQ at screening		
<40	11/168 (7)	2/157 (1)
40 to <55	17/200 (9)	7/181 (4)
≥55	19/251 (8)	13/287 (5)
CRP		
<3	17/275 (6)	7/279 (3)
3-10	16/219 (7)	8/225 (4)
>10	15/113 (13)	6/113 (5)
MRC score		
0-2	36/435 (8)	13/406 (3)
3-4	14/223 (6)	11/259 (4)
BDI		
0-4	20/190 (11)	8/225 (4)
5-6	17/287 (6)	8/268 (3)
≥7	12/175 (7)	7/158 (4)

Data are presented as No. of patients with pneumonia/No. in subgroup (%). BDI = baseline dyspnea index; CRP = C-reactive protein; MRC = Medical Research Council. See Table 1 and 3 legends for expansion of other abbreviations.

Table 5—*HRs for Predictors of Patients with Pneumonia*

Covariate	Comparison	HR	95% CI
Smoking status	Current vs former	1.02	0.58-1.78
Age, y	≥65 vs <65	1.57	0.91-2.70
% Predicted FEV_1	≥30 vs <30	0.83	0.42-1.63
Previous exacerbations	1 vs 0	1.25	0.61-2.55
	≥2 vs 0	1.14	0.55-2.33
BMI, kg/m^2	20 to <25 vs <20	1.39	0.56-3.44
	25 to <29 vs <20	0.85	0.31-2.34
	≥29 vs <20	0.97	0.33-2.83
SGRQ	40 to <55 vs <40	0.89	0.41-1.97
	≥55 vs <40	0.74	0.32-1.68
CRP, mg/L	3 to 10 vs <3	1.43	0.75-2.72
	>10 vs <3	2.60	1.36-5.00
MRC	3-4 vs 1–2	0.75	0.39-1.42
BDI	0-4 vs 5-6	2.31	1.23-4.35
	0-4 vs ≥7	2.17	0.98-4.78

HR = hazard ratio. See Table 3 and 4 legends for expansion of other abbreviations.

compared with those with a BDI of 5 to 6 ($P = .01$) and of 117% compared with those with a BDI of ≥7 ($P = .06$).

Discussion

Our data provide important new insights into the relationships of respiratory symptoms used to define COPD exacerbations and the occurrence of physician-diagnosed pneumonia. We found that reported symptoms increased prior to pneumonia. Patients receiving the ICS/LABA combination were more likely to have had an unresolved exacerbation before a pneumonia diagnosis. Risk factors, including increased CRP levels, were associated with increased risk of pneumonia but did not explain the greater propensity of ICS-treated patients to report pneumonia.

Like the TORCH study, pneumonia was not an anticipated adverse event when the INSPIRE study began, and no specific measures were taken to capture diagnostic information. If pneumonia involved a hospital visit, and chest radiographs were performed (64 cases), 78% were radiographically consistent with the diagnosis of pneumonia. Even allowing for this lower rate of radiographically confirmed events and the differential withdrawal on Tio, there was a statistically significant difference in the risk of experiencing pneumonia in patients receiving SFC. However, the duration of the pneumonia and pattern of resolution (identified from the DRC) were similar between treatment groups. Although three subjects in the SFC arm of the study died of pneumonia, the overall mortality was statistically significantly lower than with tiotropium,[17] and the death rate from pneumonia was not different from placebo in the larger TORCH study.[21]

The DRCs had few missing data, at least up to the time of diagnosis of the pneumonia and/or hospitalization. The symptoms recorded reliably identify COPD exacerbations.[26] These DRC data enabled us to use two related approaches to explore the relationship between exacerbations and pneumonia in a blinded analysis. Patients who received SFC were more likely to meet our a priori criteria for a treated or untreated exacerbation prior to pneumonia diagnosis than those receiving Tio. The pattern-based analysis supported this but also suggested that one-half the pneumonias during SFC treatment were associated with an ongoing or unresolved exacerbation.

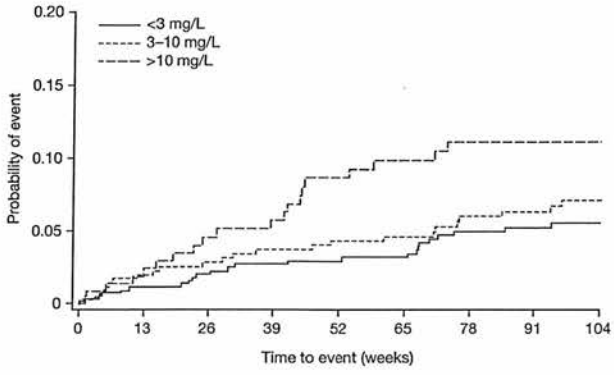

FIGURE 3. Kaplan-Meier plot of time to first pneumonia event by baseline C-reactive protein levels.

Regional differences in the reporting of pneumonia existed; whether this reflects local diagnostic custom requires a larger study to confirm. Increased breathlessness during daily activity at baseline and having a higher CRP at randomization were clearly predictive of subsequent pneumonia risk. Breathlessness is also associated with a poor prognosis independent of lung function,[27] whereas CRP is increased in other chronic diseases and may indirectly reflect the effect of comorbidity[28]; also, CRP is an independent marker of poor prognosis and hospitalization in COPD.[29] The CRP thresholds were based on the cardiovascular literature.[30] However, data from pneumonia studies have shown that high CRP levels at hospitalization predict 30-day mortality, whereas a CRP > 9.6 mg/dL on day 3 of a community-acquired pneumonia predicts late treatment failure.[31,32] Our data in patients with clinically stable COPD suggest a CRP > 10 mg/L may be a marker of pneumonia risk. Whether this reflects the presence of comorbidities or of systemic inflammation secondary to the lung disease remains unanswered. However, these risk factors were similar in each treatment group and did not explain the greater number of pneumonia reports with SFC.

Why might unresolved exacerbations be associated with pneumonia in ICS-treated patients? Incorrect diagnosis of pneumonia is possible, but unlikely, as most episodes were confirmed radiographically and the difference between Tio and ICS/LABA treatment persisted when the analysis was restricted to radiographically confirmed events. ICS use may lead the patient to delay appropriate therapy, enabling intrabronchial sepsis to progress more peripherally. This is possible, as there were few episodes in which Tio-related pneumonias were preceded by an untreated exacerbation. Inadequate antibiotic treatment might lead to some exacerbations progressing to a pneumonic illness, but this appears unlikely, as there were more exacerbations treated with antibiotics in the patients receiving SFC than in those receiving tiotropium (0.85/y vs 0.69/y, respectively).[17] Other possibilities include an effect of ICS on the patient or the infective organism, which may lead to persistent or slowly resolving infection. Detailed mechanistic studies and further clinical trials are needed to test these explanations.

Our data have limitations. Like the TORCH trialists, we did not expect to see an excess of pneumonias during treatment, so the definition of these events was less robust than those for exacerbation, our primary clinical outcome measure. However, our finding of a difference in the number of events and in the preceding exacerbation history was robust, no matter how the data were subdivided. There were fewer pneumonia events than in the longer TORCH study,[21] and the data only applied to individuals who remained in the study at the time of the pneumonia. Information about the severity, microbiology, pneumococcal vaccination, and the appropriateness of therapy received for the reported pneumonia is limited. Indeed, 16 pneumonia report patients received no antibiotics and in 34 cases antibiotics were accompanied by an oral corticosteroid. Our DRCs have been validated for COPD exacerbations rather than pneumonia, but we know of no comparable study in which symptoms have been prospectively recorded before pneumonia has developed. Given the overlap between symptoms of an exacerbation and pneumonia in COPD, we believe our data remain relevant, even though we have not captured all possible symptoms that might lead to a pneumonia diagnosis. Some of the reported and unreported events might have been pneumonias that then persisted, although the associated symptoms of those events did not suggest this and the difference between treatments still requires an explanation. Our approach was descriptive, and its objectivity was maximized by considering all symptoms before classifying them as exacerbations and relating these to the diagnosis of pneumonia. In these circumstances, post hoc statistical comparisons are not appropriate and have not been reported. Finally, our data relate only to fluticasone propionate and may not apply to other inhaled corticosteroids, such as budesonide. Whether there is a relationship between budesonide use and pneumonia is currently disputed.[20,33] We know of no equivalent data about the occurrence of prolonged symptomatic COPD exacerbations in patients with COPD treated with budesonide or of studies comparing the relative effectiveness of the different bronchodilator-corticosteroid combination products. In these circumstances, a decision about which drug to use will rely on individual clinical judgment of the relative risks and benefits of therapy.

In summary, the clinical path prior to pneumonia diagnosis in patients with COPD can be markedly

different. Some patients develop symptoms immediately prior to presentation, whereas others are diagnosed after a more protracted period of symptoms. In the INSPIRE study, these latter events are mainly seen in patients receiving ICS. Clinicians using ICS in COPD should be alert to the possibility of pneumonia developing, especially when an exacerbation is slow to recover. Future studies will be needed to define whether more active intervention in these circumstances can prevent these infrequent but potentially important events.

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Dr Calverley: contributed to developing the study protocol, was a study investigator, interpreted study data, wrote and reviewed drafts of the manuscript, and approved the final version of the manuscript.

Dr Stockley: contributed to developing the study protocol, was a study investigator, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript.

Dr Seemungal: contributed to developing the study protocol, interpreted study data, developed the first draft of the manuscript, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript.

Dr Hagan: contributed to developing the study protocol, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript.

Ms Willits: contributed to performing statistical analysis and interpreting data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript.

Dr Riley: contributed to developing the study protocol, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript.

Dr Wedzicha: contributed to developing the study protocol, was a study investigator, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript.

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CHEST Online Supplement

Reported Pneumonia in Patients With COPD

Findings From the INSPIRE Study

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e-Appendix 1.

Definition of a pneumonia

The Steering Committee defined three types of pneumonia event before reviewing the daily record card (DRC) data.

- **Pneumonia following health care utilization (HCU) exacerbation:** an episode preceded by an HCU exacerbation that continues up to start of the event or resolved < 5 days before the event

- **Pneumonia following untreated exacerbation as identified by symptom definitions:** an episode preceded by a symptom-defined exacerbation that continues up to start of the event or resolves < 5 days prior to the event but with no associated HCU exacerbation within 5 days of event

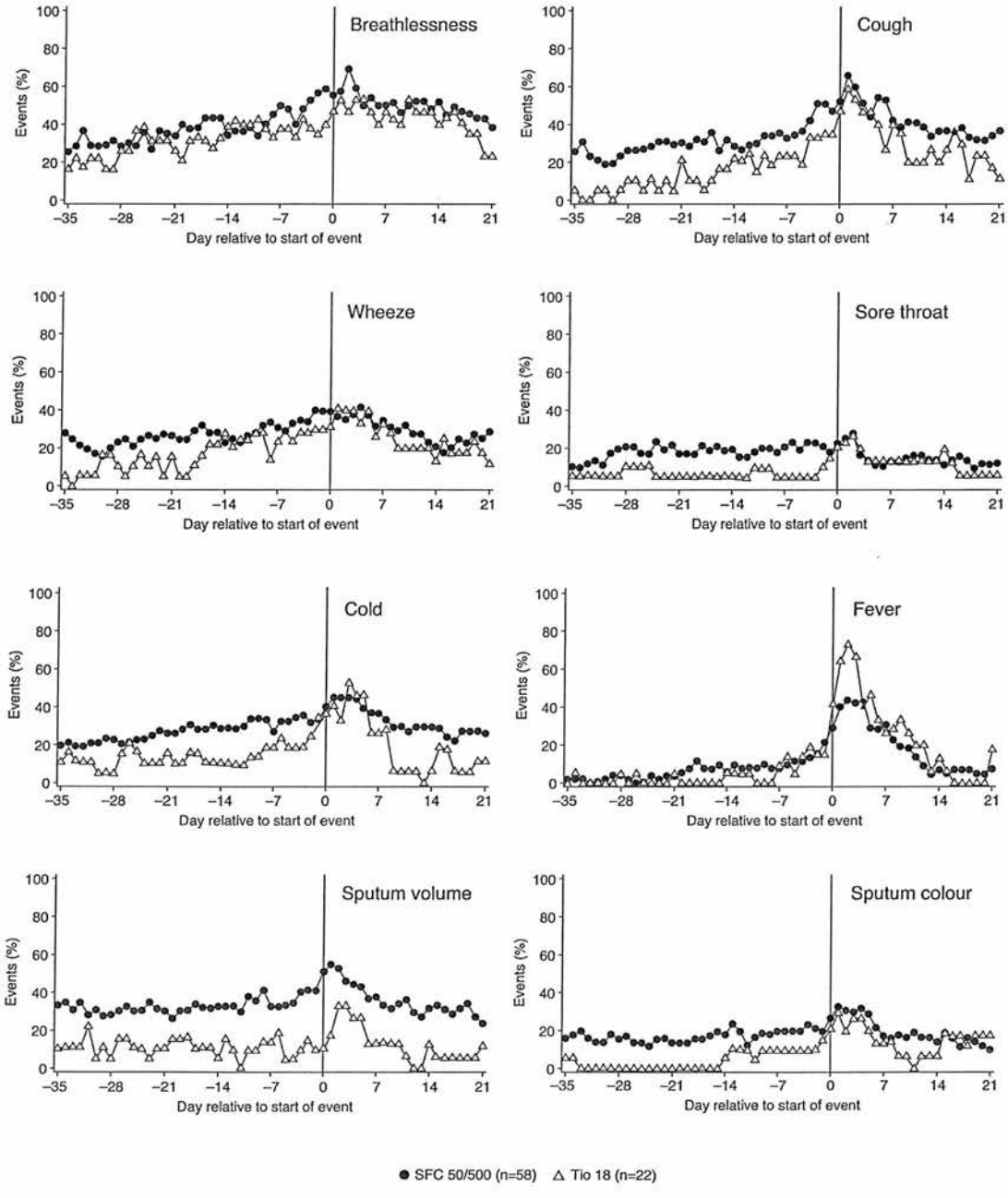
- ***De novo* pneumonia:** abrupt onset and more than 5 days from any symptomatically defined exacerbation. This may be preceded by occasional unsustained symptoms that do not meet the a priori definition of an exacerbation.

Definition of a prodrome event

A prodrome was defined in this study as the symptoms up to 35 days prior to the pneumonia event. Using this system six types of pneumonia reports were defined as described.

- HCU exacerbation which resolved prior to pneumonia
- HCU exacerbation which was unresolved at the onset of the pneumonia
- Untreated exacerbation which resolved prior to pneumonia
- Untreated exacerbation which was unresolved at the onset of the pneumonia
- *De-novo* – No consistent pattern of symptoms prior to pneumonia
- Insufficient data to characterize the pneumonia

e-Figure 1.



e-Figure 2.